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THE AMELIORATIVE EFFECT OF ANTIBIOTICS ON NONLIPOID RETICULOENDOTHELIOSIS (LETTERER-SIWE DISEASE) IN IDENTICAL TWINS

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LETTERER-SIWE disease is categorized as a nonlipoid reticuloendotheliosis, in contradistinction to Schüller-Christian disease, which is classified as a general xanthomatosis. The etiology of the disease is unknown.

During the past thirty months we have studied identical male twins who simultaneously developed Letterer-Siwe disease at the age of 9 months. It was noted that a short course of aureomycin in one of the children was associated with decrease in size of some bone lesions, fall in temperature, and general clinical improvement, while at the same time roentgen therapy to an isolated skull lesion in the other twin was without favorable general effect. An unusual opportunity occurred for careful studies with antibiotic therapy, using one of the twins alternately as a control.

The cases are reported at this time in order that further information regarding similar therapy in additional patients with this rare disease may become available from other clinics.

CASE REPORTS

Identical male twins, Peter and Paul, aged 9 months, were referred* to the Laboratory of Experimental Oncology on Jan. 7, 1949, with the chief complaint of swollen cervical lymph nodes of three months' duration. The illness began in both children within a few hours of each other.

History of Present Illness.—Paul: On Oct. 7, 1948, the child developed symptoms of a mild upper respiratory infection. Three days later he suddenly developed generalized facial swelling which lasted for a few hours, subsided, reappeared next day, and then disappeared. A skin eruption, consisting of large, red, slightly elevated irregular patches on the trunk and face, appeared at the same time and disappeared within three days. The throat was noted to be acutely inflamed. An irregular, persistent fever of 38° to 39° C. appeared shortly after the onset of the illness.

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As the facial swelling subsided, swellings were noted in the preauricular region. One week later, there was also enlargement of the postauricular and cervical lymph nodes. Axillary and inguinal adenopathy appeared some two months later, and all nodes gradually increased in size. Pallor and anemia, and failure to gain in weight became manifested within a month after onset. The boy weighed 7.9 kilograms on Sept. 27, 1948, and 8.0 kilograms on Dec. 6, 1948.

Peter: The history was practically identical with that of his twin. After a mild upper respiratory inflammation of two or three days' duration, he developed mild but definite swelling of the face. There was no accompanying rash and the swelling disappeared within a few hours. The preauricular nodes became swollen, but were less marked than in Paul. The postauricular and cervical nodes enlarged during the following week. Enlarged axillary nodes were noted two months later, but no inguinal swellings appeared. There was the same irregular fever, with elevations of temperature of 38° to 39° C. Pallor was less marked than in his twin, and he continued to gain weight, from 8.1 kilograms on Sept. 27 to 8.6 kilograms on Dec. 27, 1948.

Initially, the preauricular swellings in the children led to a tentative diagnosis of mumps. Further studies revealed a definite hypochromic, normocytic anemia, and bone marrow aspirations showed an increased percentage of small lymphocytes in both children. A tentative diagnosis of lymphocytic leucemia was made.

Treatment during the first three months of illness included sulfonamides for four days at the time of onset and 100,000 units of penicillin daily for two days. Oral penicillin was administered for a few days later during the course of illness. Both children also received iron for two months and folic acid for one month before entry, and were exposed to sun lamp therapy for one month.

Past History.—The twins were born on March 28, 1948. The prenatal course and delivery were normal. Their weights at birth were 2.9 kilograms for Paul and 3.1 kilograms for Peter. The obstetrician confirmed that there had been a single placenta and amniotic sac, and footprints showed practically identical mirror patterns. The twins were placed on formula feedings. Their weight and development were normal until the onset of the present illness.

Both children had clubfeet, treated by application of casts during the first six weeks with good results. Peter's deformity was bilateral, whereas Paul's was limited to the left side. Peter had a port-wine stain over the right side of the head and neck, which faded considerably during the following nine months.

At 6 months of age, the twins were noted to have rasping respirations. Roentgenograms of the chest demonstrated widening of the mediastinal shadow, presumably due to enlargement of the thymus. Both received radiation treatment with prompt disappearance of the symptoms.

Both children had received immunizations against smallpox, pertussis, diphtheria, and tetanus. They had had no childhood infections.

Family History.—There was no family history of blood dyscrasias, cardiac, pulmonary, or renal disease. There were no other siblings.

Physical Examination.—Paul: Paul appeared to be the sicker of the twins. He was a well-nourished, well-developed 9-month-old, white, red-haired boy. He was alert and responsive, sat up fairly well but did not stand.

The temperature was 37.6° C., pulse 150. Head circumference was 45 cm., length 70 cm., weight 8.0 kg. The skin was clear.

There was marked generalized lymph node enlargement, particularly in the posterior occipital, anterior cervical, submental, post- and preauricular areas. The axillary and inguinal nodes were also enlarged. The nodes were resilient, not matted, nor tender (Fig. 1*A*).

A. *B.*

C.

Fig. 1.—*A*, Paul, Jan. 11, 1949. Note generalized adenopathy and periorbital swelling. *B*, Peter, Jan. 11, 1949. Note generalized adenopathy and periorbital swelling. *C*, Paul and Peter, June 5, 1951. Difference in height may be accountable on basis of collapsed ninth thoracic vertebra in Peter (right).

TABLE I. HEMATOLOGICAL FINDINGS

PAUL

DATE	PERIPHERAL BLOOD					BONE MARROW (200 CELLS)				
						GRANULOCYTES				
	HEMOGLOBIN PER 100 C.C. (GM.)	WBC X 10^3/CMM. (NO.)	PMN (%)	LYMPHOCYTES (%)	EOSINOPHILS (%)	PMN (%)	BANDS (%)	MYELOCYTES (%)	PME (%)	LYMPHOCYTES (%)
10/48	5.8	12.1	70	30						
12/48	6.5	6.6	66	29	1					
1/49	8.2	8.9	74	26						
2/49	8.5	10.85	73	24		20	8.5	23	9	38
3/49	8.2	7.55	72	25						
4/49	8.6	6.1	75	25						
5/49	9.8	7.15	55	45						
6/49	10.1	7.9	42	58						
9/49	10.1	8.6	52	48		13	3.5	16.5	3	53
11/49	10.4	5.7	62	38	13					
12/49	11.4	6.5	54	46		10.5	7	28	3.5	45.5
1/50	11.5	8.4	53	47						
2/50	11.6	7.3	36	64						
3/50	12.2	6.15	55	40	3	12	9	9	4	62.5
4/50	10.9	6.5	41	49	6					
5/50	12.5	6.8	55	38	1					
6/50	14	9.85	31	68	1	24	2.5	4		29
7/50	14	8.4	58	37	3					
8/50	11	7.0	64	28	5					
9/50	11.8	6.0	58	37	1	16.5	1.5	5	1	73.5
10/50	11.4	7.5	51	36	5					
11/50	12.7	9.6	52	37	4					
12/50	12.7	7.35	42	46	2					
1/51	13.4	7.35	37	62	1	16.5	9	18.5	3.5	51.5
3/51	10.9	7.15	52	41						
4/51	11.9	11.1	52	31	3					
6/51	12.9	8.25	65	30	1	14.5	8	12.5	4.5	56
7/51	---	8.8	45	49	4					

The eyes, ears, and mouth were normal except for the presence of small hemorrhages in both fundi. He had seven teeth, and one was erupting. The neck and chest were normal. The lungs and heart were normal except for a grade 2 systolic murmur at the base.

The liver edge was not definite, but a sense of resistance was encountered 3 cm. below the costal margin. The spleen was palpable deep in the left upper quadrant; it was firm and movable. No other abdominal masses were detected. The genitalia were normal. The left foot was short, broad and thick. The reflexes were normal.

Peter: The twin was a well-nourished, well-developed boy in no acute distress. The temperature was 37.7° C., pulse 140. Head circumference was 45.5 cm., length 70 cm., weight 8.7 kg.

There was a faint but extensive port-wine stain on the right side of the head, neck, and face. Otherwise the skin was clear.

There was extensive, marked enlargement of lymph nodes, particularly in the cervical and preauricular areas (Fig. 1*B*).

The eyes, ears, nose, and mouth were normal. No hemorrhages were seen in the fundi. There were eight teeth. The neck and chest were normal. The lungs and heart were normal; no cardiac murmurs were heard.

The liver was enlarged to 3 cm. below the costal margin, with a smooth, sharp edge. The tip of the spleen was felt in the anterior axillary line, and was firm, smooth, and movable. No other masses were detected. The genitalia were normal, the extremities were normal and the reflexes were physiological.

TWINS WITH RETICULOENDOTHELIOSIS

PETER										
PERIPHERAL BLOOD					BONE MARROW (200 CELLS)					
					GRANULOCYTES					
HEMOGLOBIN PER 100 C.C. (GM.)	WBC X 10^3/CMM. (NO.)	PMN (%)	LYMPHOCYTES (%)	EOSINOPHILS (%)	PMN (%)	BANDS (%)	MYELOCYTES (%)	PME (%)	LYMPHOCYTES (%)	THERAPY
6.0	12.3	63	37							
6.5	7.2	59	40	1						*Paul:* 1/7/49 to 2/8/49 Penicillin 6,400,000
8.8	8.2	67	33	3	10.5					
7.9	7.85	72	28	3	16	13.5	25.5	4	45	
8.0	6.45	73	27			12	19.5	2	50	
8.5	8.15	61	39							*Paul:* 3/7/49 to 3/17/49 Aureomycin 10 Gm.
8.7	3.6	51	49							
10.6	5.9	54	46							
10.0	7.5	55	45		18	4.5	20	2.5	49.5	*Paul:* 10/6/49 to 11/16/49 Penicillin 8,000,000 Aureomycin 30 Gm. Chloromycetin 30 Gm.
10.0	8.85	77	23							
9.5	5.75	56	44		13.5	6.5	34.5	4	37.5	
8.8	8.4	33	67							
10.7	8.85	53	47							
10	7.9	60	31		16	5	15	4	56.5	
10	7.2	57	34	6	18	11	11	5	58	*Peter:* 12/22/49 to 2/2/50 Penicillin 8,000,000 Aureomycin 30 Gm. Chloromycetin 30 Gm.
10	7.0	40	46	2						
11	7.4	36	64		28	7	9	2	73	
13	6.5	56	34	6						
11	6.8	69	24	3						
13	6.8	53	41	1	16.5	1.5	5	0.5	73.5	
11.6	7.5	49	45	1						*Peter:* 3/24/50 to 6/22/50 Penicillin 33,000,000 Aureomycin 54 Gm. Chloromycetin 75 Gm. Dihydrostreptomycin 37 Gm.
12.2	5.9	69	29	1						
13.5	5.5	59	29	7						
12.3	4.5	38	59	2	14	6.5	11	2	66	
11.3	8.95	61	36							
11.1	6.3	72	23	5						
12.5	7.6	42	55	1	17.5	8.5	12	2	58	
11.2	9.8	58	34	4						

Laboratory Findings.—The urine of both children showed no abnormalities. The peripheral blood confirmed the presence of an anemia, which was hypochromic, normocytic in type. The hemoglobin determination on Paul was 8.2 and on Peter, 8.8 Gm. per 100 c.c. The white blood count was 8,900 and 8,800, respectively, with 26 and 33 per cent of mature lymphocytes. The bone marrow aspirations showed the presence of 40 and 32 per cent lymphocytes, respectively, in an otherwise normal marrow; the lymphocytes were small and not suggestive of a leucemic process (Table I).

Biochemical determinations of the blood included nonprotein nitrogen, total protein, thymol turbidity, phosphorus, calcium, free and total cholesterol, and amylase. All were within normal ranges. Oral and intravenous glucose tolerance curves were hypoglycemic in type in both children (Fig. 2).

Laboratory tests for infectious agents included tuberculin skin test and agglutinations for heterophile antibody, Brucella, antistreptolysin, psittacosis, lymphopathia venereum, and Q fever; all were negative. Serologic tests of the blood were negative for syphilis.

Roentgenograms of the skeletal system showed multiple punched-out areas, particularly in the skull, the femurs, pelvis, and ribs (Figs. 3*A*, 4*A*, 5*A* for Paul, and 6*A*, 7*A*, 8*A* for Peter).

A lymph node was removed from each of the twins, and a biopsy performed on one of the skull lesions. The nodes showed marked distortion of the normal follicle pattern and replacement by masses of reticuloendo-

thelial cells. There were also large numbers of eosinophils and occasional giant cells. The reticuloendothelial cells had a stellate shape with basophilic cytoplasm and large irregular nuclei. The giant cells had numerous small nuclei and sparse basophilic cytoplasm (Fig. 9). Sections from the skull lesion revealed a similar picture with considerable necrosis and many polymorphonuclear cells.

The diagnosis on both twins was reticuloendotheliosis, consistent with Letterer-Siwe's disease.

6.4 million units. In February, 1949, twenty days after completion of penicillin, the lesions in the femora and skull appeared to progress roentgenologically. Between March 7 and 17, he was given daily oral doses of 1 Gm. of aureomycin, for a total dose of 10 Gm.

By April, a month after the administration of aureomycin, it was noticed that the osteolytic lesions of the femurs had become smaller and fewer in number. There was an increase in the number and size of the skull lesions,

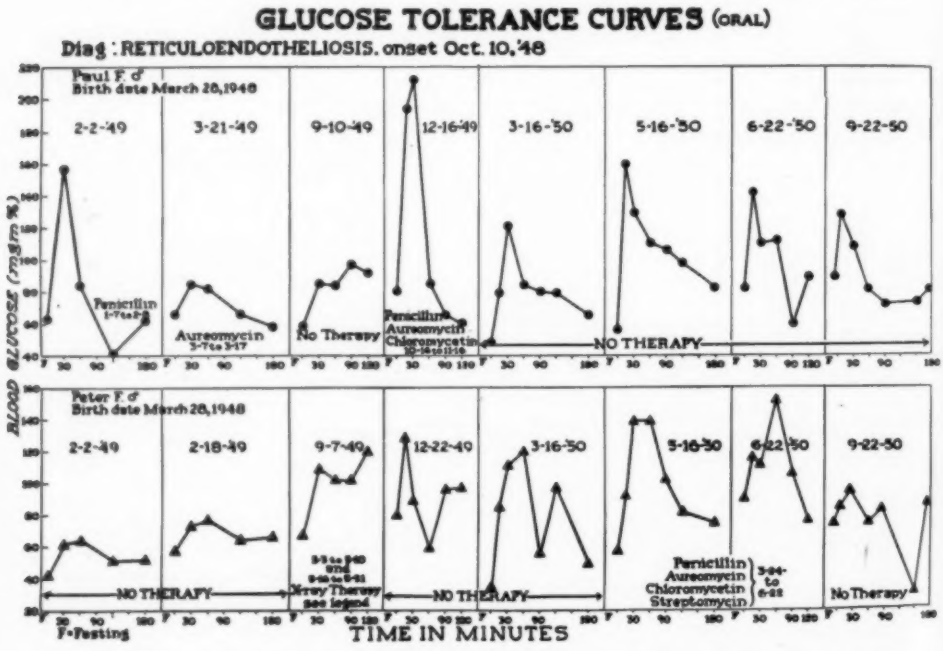


Fig. 2.—Glucose tolerance curves following 3 Gm. of glucose orally per kilogram body weight. Note apparent increased peaks during treatment with antibiotics.

Treatment.—Since the history suggested an infectious component in the illness of the twins, and since Paul appeared to be the sicker of the two children, it was decided to treat Paul with antibiotics while maintaining Peter as an untreated control.

Paul received 200,000 units of repository penicillin daily from Jan. 7 to Feb. 8, 1949, for a total dose of

but the edges of some of the lesions were slightly obscure as compared with earlier films (Fig. 3*B*).

In June, 1949, the skull lesions became definitely smaller and fewer in number (Fig. 3*C*). The appearance of the femurs by September was strikingly improved (Fig. 5*B*).

During this time the clinical improvement in Paul was rather definite,

although temporary, lasting about two months. The lymph nodes were definitely reduced in size, and the spleen became impalpable. He was more alert, and gained weight. A glucose tolerance curve performed on June 22 showed a more normal rise than was originally evident (Fig. 2).

The observed response encouraged another course of more intensive therapy for Paul. Between Oct. 6 and Nov. 16, 1949, he received aureomycin and Chloromycetin, 1 Gm. each, orally, for thirty days, for a total dose of 30 Gm. of each antibiotic. To this was added 400,000 units of repository peni-

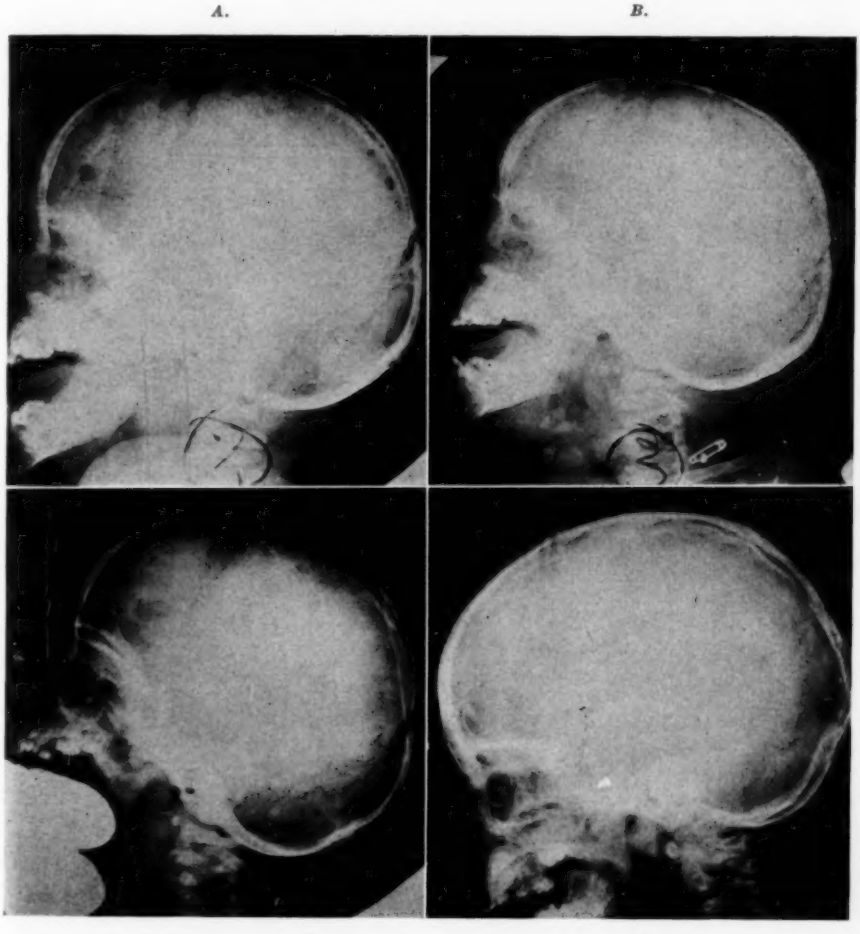


Fig. 3.—Roentgenograms of the skull on Paul. *A*, Feb. 28, 1949. Multiple, irregular radiolucent areas of bone destruction scattered throughout the skull, most prominent in the parietal area. No periosteal reaction is seen. *B*, April 27, 1949. Increase in the number and size of lesions; the edges of some lesions are less sharply demarcated. Forty days after first ten-day course of aureomycin. *C*, June 30, 1949. Definite regression of lesions. About 100 days following first course of aureomycin. *D*, June 5, 1951. No sharply defined lesions are seen. The frontal irregularity in the thickness of the bones produces a beaten-silver appearance to the skull.

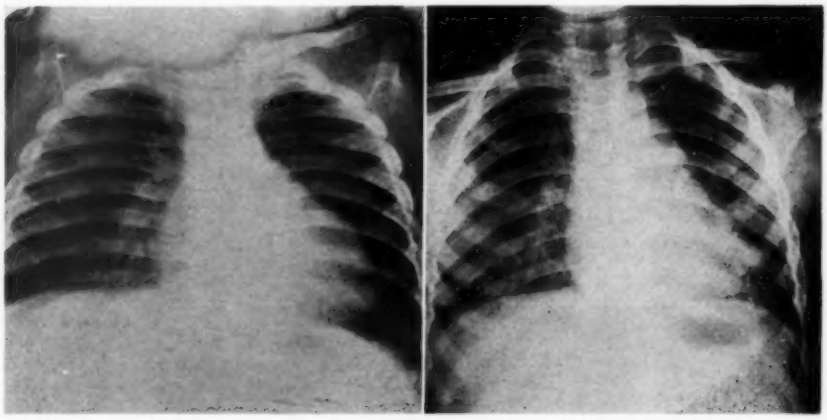
cillin given every other day for total of eight million units.

By December, 1949, the improvement in the radiographic lesions in Paul was striking. The clinical condition was also greatly improved, with the lymph nodes being small and shotty. The hemoglobin increased from approximately 10 Gm. to 11.4 Gm. The glucose tolerance curve became more normal.

Between January and December, 1949, Peter received no treatment with antibiotics. He received x-ray treatment to the skull lesions in May, 1949, spleen remained palpable. The hemoglobin did not rise above 10.6 Gm., and the glucose tolerance curve remained hypoglycemia.

The definite response in Paul, and the serious progression of the disease in Peter required reconsideration of the original therapeutic plan. It was decided to treat Peter and to stop further therapy in Paul.

Peter was, therefore, treated on an out-patient basis between Dec. 22, 1949, and Feb. 2, 1950, with penicillin, aureomycin, and Chloromycetin. The total dosage of penicillin during this period was eight million units, but only 30



A. *B.*

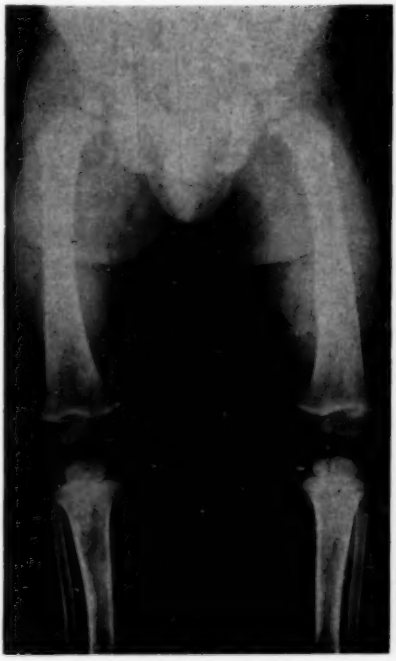
Fig. 4.—Roentgenograms of the chest on Paul. *A*, March 29, 1949. No evidence of parenchymal pulmonary lesions. The ribs and scapulae show abnormality in bone structure. *B*, June 5, 1951. Widening of superior mediastinum, constant since first noted in January, 1950. The bony structure has been within normal limits since November, 1949.

six treatments using 100 Kv apparatus. A tissue dose of 560 r was given through a 7 × 7 cm. ports to left and right preauricular areas during six days. A tissue dose of 770 r was delivered through a 7 × 7 cm. ports to each of right and left frontal areas during sixteen days. The osteolytic lesions in the femurs, ribs, humerus, and scapula showed definite progression in size and in number, although the skull lesions showed a definite effect (Fig. 6*C*). Clinically he began to fail. The lymph nodes remained of approximately the same size and the Gm. each of aureomycin and Chloromycetin were tolerated by the child.

By March, 1950, there was definite evidence of disappearance and improvement in the bone lesions in Peter. The hemoglobin level, however, was approximately 9 Gm. Paul's roentgengrams at this time also showed continued improvement.

The bone marrow in both children continued to show over 50 per cent lymphocytes. The glucose tolerance tests were still abnormal in that there was only a brief rise of the blood glucose at thirty minutes with a rapid

A.



B.

C.

Fig. 5.—Roentgenograms of the pelvis on Paul. *A*, Jan. 17, 1949. The pelvis and the femurs show multiple rarefied areas, particularly above the acetabula and throughout the femurs. These lesions became more extensive in February. *B*, Sept. 13, 1949. Marked clearing of lesions except for an area of decreased density at the junction of the middle and lower right femur and possibly in medullary cavity in left femoral shaft. Also note lesions in tibia. Six months following first course of aureomycin. Improvement was first noted during April, 1949. *C*, June 5, 1951. The femurs, pelvis, and tibia are roentgenologically within normal limits. Growth, development, and trabecular pattern are normal.

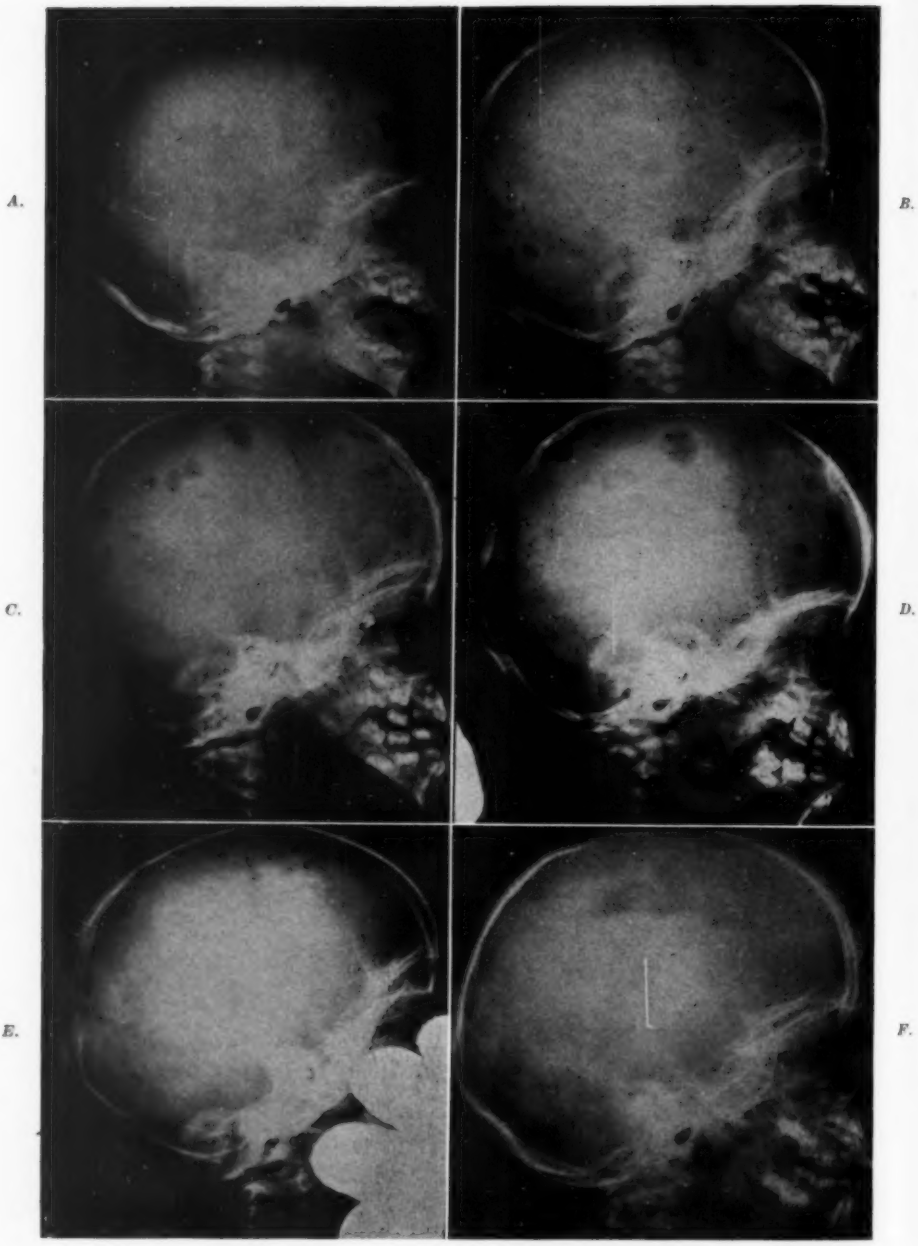


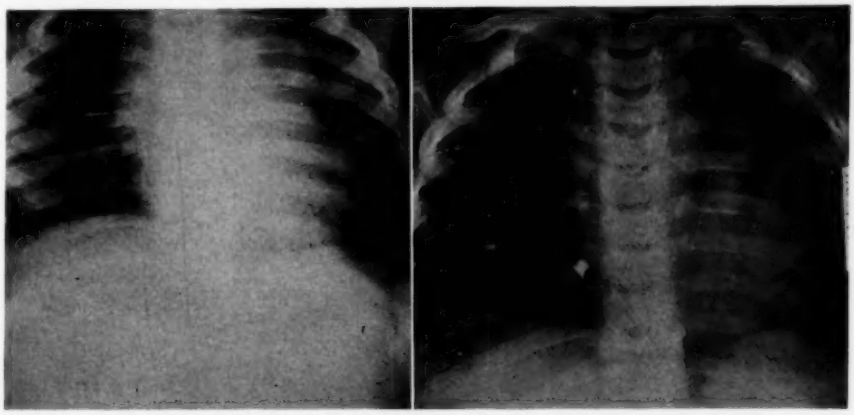
Fig. 6.—Roentgenograms on skull of Peter. *A*, Jan. 17, 1949. Large number of radiolucent, punched-out lesions, particularly in the frontal region, and one large occipital lesion. *B*, April 27, 1949. Progression of lesions in size and in number. *C*, Dec. 5, 1949. Marked regression of some lesions in the previous sites, but a number of new lesions have appeared in the parietal and frontal regions. X-ray therapy to the frontal area of the skull was delivered in May, 1949, for a total tissue dose of 770 r. *D*, Feb. 18, 1950. Decrease in number and size of lesions with marked bone reaction at the edges of the lesions. Two weeks after completion of first course of therapy with aureomycin, Chloromycetin, and penicillin. *E*, June 27, 1950. Progressive regression in the lesions. One week after completion of second three-month course of antiobiotic therapy. *F*, June 6, 1951. No evidence of localized lesions remains. The calvarium shows variation in bone density.

fall to the low base line. Previously, Paul's glucose tolerance test had been closer to normal (Fig. 2).

Since Peter's improvement had been less than anticipated and administration of the medications at home had been unsatisfactory, he was hospitalized on March 24, 1950. On this admission, Peter was somewhat restless, irritable, and had little or no appetite. Physical examination was not remarkably different from that on the initial admission. Collapse of the ninth thoracic vertebra was observed roentgenographically, but no kyphosis was evident on examination, and he stood and walked normally.

prothrombin levels and bleeding times were unaltered during the period in which the stools were free of the normal bacterial flora.

Peter tolerated the medications except for aureomycin, which had to be reduced from 1.0 to 0.5 Gm. per day because of nausea and emesis. He had been receiving the medications for approximately one month when jerky, irregular motions of the upper extremities were noted in the early mornings. No neurological changes were found, and the condition did not improve when the dihydrostreptomycin was stopped for a short period. A fasting glucose level at this time was 35 mg.



A. *B.*

Fig. 7.—Roentgenograms of chest on Peter. *A*, Sept. 13, 1949. Widening of the superior mediastinum, without parenchymal abnormality. The ribs have abnormal pattern and appear to be widened. These abnormalities were observed originally in January, 1949. *B*, June 6, 1951. Some decrease in the mediastinal shadow. The ribs and other bony structures remained within normal limits, since September, 1950.

From March 24 to June 22, 1950, Peter received the following antibiotics: dihydrostreptomycin, 37 Gm. in seventy-five days and repository penicillin, 33 million units in eighty-two days, administered intramuscularly; aureomycin, 54 Gm. in eighty-six days and Chloromycetin, 75 Gm. in eighty-seven days, orally.

Stool cultures on Peter during this therapy revealed numerous *Pseudomonas aeruginosa* colonies[4] and an occasional colony of enterococcus viridans. No other bacteria grew. The per cent, and when early morning feedings were instituted, the peculiar motions disappeared and did not recur when dihydrostreptomycin was resumed.

Subsequent Course.—The twins have been observed and studied at regular intervals up to September, 1951. The clinical appearance of the twins was essentially identical at that time.

The general course of the disease in both children has been one of marked progressive improvement, although a few new lesions were observed to ap-

A. C.

B. D.

Fig. 8.—Roentgenograms of pelvis and femurs, Peter. *A*, Feb. 20, 1949. Extensive rarefied areas in the pelvis and femurs. *B*, Sept. 26, 1950. Definite increase in density of the pelvic and femoral bones. There is a new lesion in the distal end of the right femur, first seen in May, 1949. Three months following completion of antibiotic therapy. *C*, June 6, 1951. The bone above the left acetabulum still shows evidence of rarefaction, but is less evident than before. *D*, June 6, 1951. The femurs are within normal limits, since completion of first course of antibiotics in February, 1950.

pear, particularly in the skull. Objective evidence of improvement consisted of marked decrease in hepatosplenomegaly, disappearance of lymphadenopathy, rise in hemoglobin and erythrocytes, and roentgenographic evidence of recalcification, decrease in number and disappearance of many of the osteolytic lesions of the skeleton. Paul has maintained this improvement for twenty-three months since his last therapy in November, 1949. Peter is now fifteen months post-treatment and also remains apparently well (Fig. 1*C*).

The intravenous glucose tolerance curves after the antibiotic therapy in both children showed changes toward normal as compared with the original hypoglycemic response (Fig. 2). Lymph node biopsies from the small nodes available after therapy showed few reticulum cells with marked fibrosis and scarring as compared with the original biopsies taken before antibiotics were started.

Laboratory determinations up to June, 1951, revealed the urine to be normal. The nonprotein nitrogen, total protein, thymol turbidity, phos-

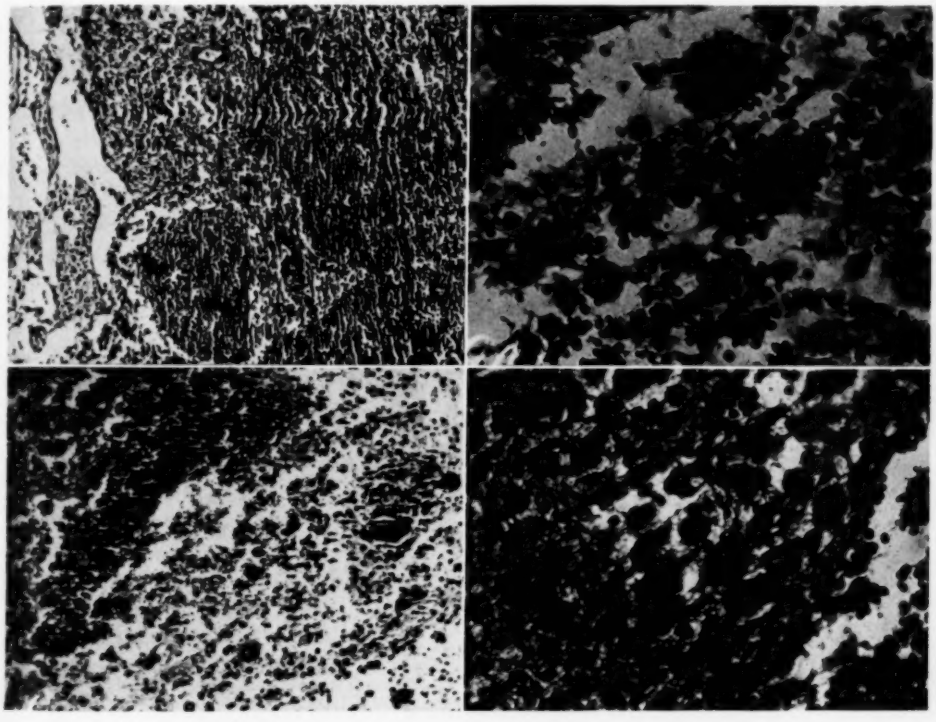


Fig. 9.—*A*, Paul, March 2, 1949. Note reticular hyperplasia with preservation of follicular structure. (Hematoxylin and eosin, ×100.) *B*, Higher magnification, showing histiocytes and giant cells. (Hematoxylin and eosin, ×460.) *C*, Peter, Feb. 9, 1949. Showing same structure. (Hematoxylin and eosin, ×100.) *D*, Higher magnification showing histiocytes and giant cells. (Hematoxylin and eosin, ×460.)

phorus, calcium, and free cholesterol of the blood were all within normal limits.

The weight curves showed acceleration of gain following the administration of the antibiotics (Fig. 10). The bone marrow and peripheral blood counts have shown a persistent lymphocytosis (Table I). The bone marrow aspiration in June, 1951, revealed some large clasmatocyte-like cells with a foamy cytoplasm.

DISCUSSION

The occurrence of nonlipoid reticuloendotheliosis in identical twins has not been reported. A description of this

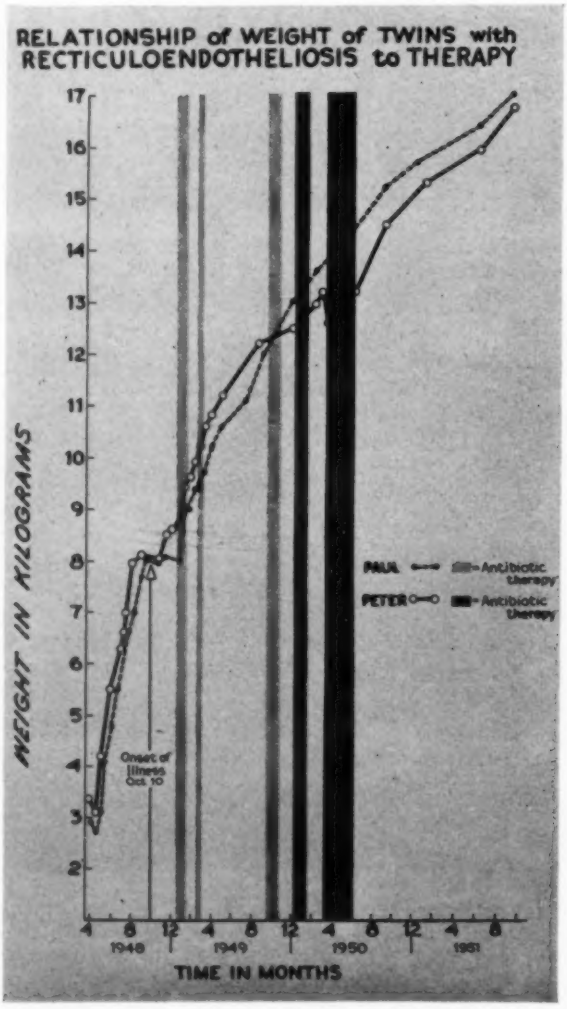


Fig. 10.—Relationship of weight of twins with reticuloendotheliosis to antibiotic therapy.

disease in one of nonidentical twins has appeared; the remaining twin showed no evidence of disease.[3]

The practically simultaneous development of the disease in both twins is well documented by the parents, and by pediatricians to whom they promptly took the children. The appearance of the condition in both children under these circumstances might be considered to be suggestive of an infectious etiology. Siwe[2] believed this illness to be nonhereditary and nonfamilial and in the thirty-two cases reported since Letterer's original accurate description of this state in 1924,[5] this is the first reported instance of such a familial occurrence.

The favorable response of this disease to combined antibiotic therapy may have been due to an effect upon some infectious agent. It is possible, however, that some change in metabolism due to the absence of normal flora in the stool[4] may have contributed to the observed improvement. Despite the encouraging improvement of both children following antibiotic therapy, the roentgenographic findings afford objective evidence that the disease process or its sequelae remain. It must also be emphasized that the duration of this disease is known to be variable with a course lasting weeks or months. The survival of other patients reported has not exceeded two years, however.

Aronson[6] recently reported the favorable response of an 18-month-old child diagnosed Letterer-Siwe's disease, following streptomycin therapy for five weeks. The diagnosis was based primarily on the spleen removed surgically to ameliorate a hemolytic anemia allegedly due to hypersplenism. Pathological examination of the spleen originally suggested sarcoidosis. While streptomycin was included as one of the four antibiotics administered in these two cases, it should be noted that the original improvement noted in Paul occurred following penicillin and aureomycin before any streptomycin had been given. Penicillin alone had failed to produce any improvement.

It is also entirely possible that only those patients associated with an acute infection at the onset may respond similarly to this therapy and those without any etiologically significant infection may or may not to likewise. The infrequency of this disease precludes any single group of investigators accumulating a conclusive series under such therapy and control to establish the true value of such antibiotic therapy. This preliminary note is reported, therefore, in the hope that other cases will receive similar therapy and observations to permit thorough evaluation of such therapy. The future course of these twins will be observed closely and reported at a later date.

CONCLUSIONS

1. The simultaneous occurrence of nonlipoid reticuloendotheliosis (Letterer-Siwe's disease) in identical male twins is reported.

2. The treatment of each child separately with a combination of aureomycin, Chloromycetin, streptomycin, and penicillin and employing the other twin as a control afforded a unique opportunity to evaluate objectively the effectiveness of these antibiotic combinations upon the disease.

3. In both twins, the administration of this combination of antibiotics was followed by marked clinical improvement, associated with disappearance of hepatosplenomegaly, lymphadenopathy, regression of anemia and roentgenographic evidence of healing and disappearance of osteolytic lesions.

4. Although both children now appear well, fifteen and twenty-three months after antibiotic therapy, evidence of residual disease and sequelae remain and the preliminary character of this report is emphasized.

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FLUSH METHOD FOR BLOOD PRESSURE DETERMINATIONS IN NEWBORN INFANTS

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THE inherent difficulties in the auscultatory method for obtaining blood pressures in infants are quite obvious; in fact, the difficulty of keeping the baby quiet, hearing the pulse beat, finding the correct sized cuff, and the time consumed in using this method for routine physical examination of the normal infant make this conventional method most impractical. The blood pressure studies in newborn infants by Woodbury, Robinow, and Hamilton[1] by optical registration using a hypodermic manometer are quite complete and adequate, but the elaborate technique involved would limit its routine clinical use. There is, however, a necessity for the accurate determination of blood pressures in infants suspected of having coaretation of the aorta, congenital anomalies of the kidney, metabolic disturbances, such as potassium deficiency and hypoglycemia, and in babies born of toxemic and diabetic mothers. It was this need for a simple but moderately accurate method for blood pressure determinations in newborn and older infants that prompted the application of the method of digital blood pressure as described by Weaver and Bohr.[2]

The 2.5 cm. cuff was selected for newborn infants as advised by Woodbury, Robinow, and Hamilton.[1] The cuff is placed around the ankle or wrist in the usual manner and a piece of rubber sheeting or old rubber glove is wrapped snugly around the foot or hand, starting distally, so that the blood is pressed from the extremity. The cuff is then inflated to a pressure slightly above the suspected systolic pressure, the rubber bandage is then removed from the blanched extremity, and the pressure is slowly reduced in the cuff. The approximate systolic pressure is the reading at which blood re-enters the foot or hand, causing a sudden flush (Fig. 1).

There are a number of details in the method which should be stressed so that optimum readings may be obtained. Care should be taken to keep the baby quiet and a feeding of water or the use of a pacifier seems most effective. Good lighting is imperative. The use of a cuff of proper width has been stressed, and the pressure in the cuff should be released not faster than 6 to 7 mm. per second. This rate was determined as optimal by comparing the results of ten blood pressure determinations in each of four extremities in twelve newborn infants. The pressure in the cuff was released slowly five times and rapidly five times. It can be seen from Table I that fairly consistent results were obtained when the pressure was released not faster than 6 to 7 mm. per second. Readings varied widely when the pressure in the cuff was released rapidly.

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Since infants could not be used for the comparison of this flush method with the techniques of auscultation and palpation, older, more cooperative children were selected. Comparison of the three methods was made on seven children with normal blood pressures (Table II), three with hypertension (Table III), and three with coaretation of the aorta (Table IV).

In Table II the bracketed readings were taken by two different observers. From the results, it can be seen that pressures obtained by the flush method are somewhat lower than those by auscultation and palpation. Similar results are recorded in Table III in children with hypertension.

In Table IV are the pressures of children with coaretation of the aorta (diagnosis verified by surgery). In two of these subjects it was possible to obtain pressure in the lower extremities by the flush method but not by auscultation. The third subject was only nine days old and pressures, even in the upper extremities, could be obtained only by the flush method, which also was satisfactory for determination of lower extremity blood pressures.

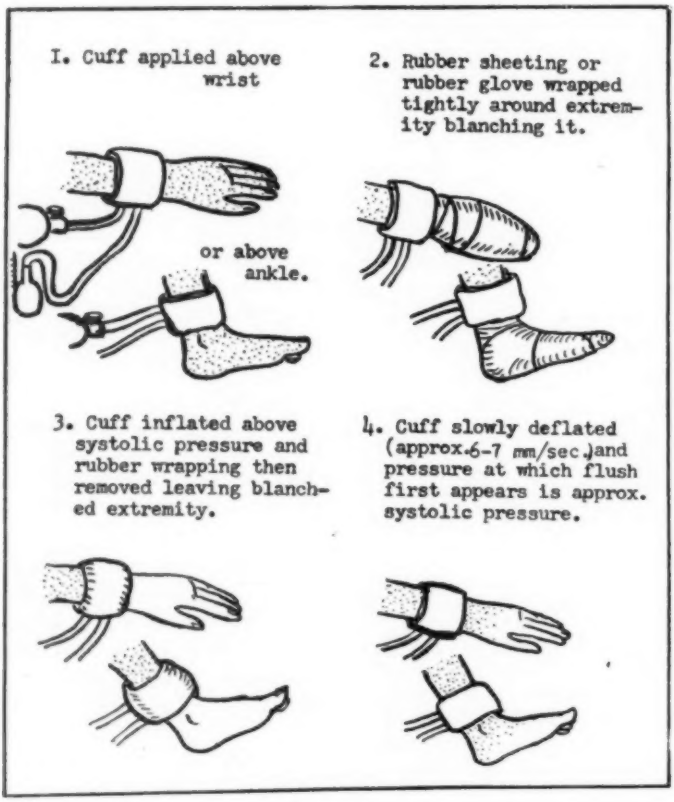
1. Cuff applied above wrist
or above ankle.
2. Rubber sheeting or rubber glove wrapped tightly around extremity blanching it.
3. Cuff inflated above systolic pressure and rubber wrapping then removed leaving blanched extremity.
4. Cuff slowly deflated (approx.6-7 mm/sec.)and pressure at which flush first appears is approx. systolic pressure.

Fig. 1.

TABLE I. BLOOD PRESSURE IN NEWBORN INFANTS BY FLUSH TECHNIQUE

SUBJECT	ARM				LEG			
	LEFT		RIGHT		LEFT		RIGHT	
	B.P.	RATE OF RELEASE OF PRESSURE IN CUFF MM. PER SECOND	B.P.	RATE OF RELEASE OF PRESSURE IN CUFF MM. PER SECOND	B.P.	RATE OF RELEASE OF PRESSURE IN CUFF MM. PER SECOND	B.P.	RATE OF RELEASE OF PRESSURE IN CUFF MM. PER SECOND
Baby N.	82	4	86	4	70	5	78	5
	84	4	88	4	78	3	76	4
	94	2	90	4	78	3	80	6
	96	2	92	3	80	4	82	6
	88	7	92	3	78	5	74	5
Baby L.	62	3	56	8	50	6	50	7
	60	3	66	7	52	6	58	7
	54	6	68	9	48	5	58	6
	64	6	64	5	46	5	62	6
	62	4	66	7	52	6	58	5
Baby P.	80	3	82	8	70	6	80	6
	88	5	86	6	82	4	78	9
	78	5	84	8	92	3	88	7
	86	5	86	6	96	4	100	5
	82	5	92	5	90	6	100	6

TABLE II. COMPARISON OF READINGS BY AUSCULTATION, PALPATION, AND FLUSH METHODS IN OLDER CHILDREN WITH NORMAL BLOOD PRESSURES

SUBJECT	AUSCULTATION	PALPATION	FLUSH
C. O'N., WF 3 yr.	110 110	120 100 100	112 118
	108 106	120 100 100 120 96	106 100
R. B., WM 7 yr.	116 114	118 116	102 102
	118 120	114 116	108 108
L. B., WF 4 yr.	108 108	108 108	96 100
	109 109	109 109	108 96
J. T., WF 3 yr.	84 86 84 83	80 80 90 88	72 74 72 80
B. W., WF 5½ yr.	108 116 113 112	108 102 114 112	102 104 104 112
D. H., WM 4¾ yr.	110 106	102 102	100 104
	102 102	96 96	86 90 96
A. B., WM 5½ yr.	108 110	108 110	96 95
	116 112	108 102	108 108

TABLE III. COMPARISON OF AUSCULTATION, PALPATION, AND FLUSH READINGS IN OLDER CHILDREN WITH HYPERTENSION

SUBJECT		AUSCULTATION	PALPATION	FLUSH
L. H., WF	Rt. Arm	250/200	236	260
4½ yr.		245/190	240	240
		235/180	238	262
		235/180	255	261
		240/190	250	251
		242/198		
	Rt. Leg	280/200	280	260
		280/220	290	280
		285/200	285	280
		285/225	290	265
		290/200	285	285
S. K., WM	Lt. Arm	135/90	130	127
3 yr.		132/90	130	120
		132/89	130	120
		130/88	130	118
		129/88	128	116
	Lt. Leg	140/100		120
		140/100		120
		134/98	Unable to palpate	128
		141/100		125
		141/98		130
J. H., WM	Arm	136⎫	132⎫	128⎫
3 yr.		136⎭	140⎭	134⎭
		144⎫	130⎫	130⎫
		144⎭	130⎭	140⎭

TABLE IV. BLOOD PRESSURES IN CHILDREN WITH COARCTATION

SUBJECT		RIGHT ARM	LEFT ARM	RIGHT LEG	LEFT LEG
J. P., WF	Aus.	140/110	95/?	Unable to obtain	
3½ yr.	Flush.	165	115	80	90
P. F., WF	Aus.	160	160, 165	Unable to obtain	
2½ yr.	Flush.	140, 142	145, 150	72, 72	72, 72, 52
R. D., WM	Flush.	64	68	28	36
9 days					

The diagnosis in this infant was verified by necropsy. A brief summary of this third case follows:

R. D., a 9-day-old white male, was admitted because of acute respiratory distress and cyanosis of eighteen hours' duration. The parents had noticed that the baby's respirations were short and rapid. He appeared acutely ill with marked cyanosis of the lips and nail beds. The heart rate was regular and no murmurs were heard. Neither femoral pulse could be palpated. Fluoroscopy revealed clear lung fields and a globular-shaped heart with possible slight enlargement. The liver was palpable one and one-half fingerbreadths below the right costal margin. Blood pressures by the flush method were 68 mm. Hg in the left arm, 36 mm. in the left leg, 64 mm. in the right arm, and 28 mm. in the right leg.

Approximately thirteen hours after admission, respirations suddenly became more rapid and the liver descended three fingerbreadths below the right costal margin. Repeat fluoroscopy showed the heart enlarged to the left with a straightened left border. The baby was rapidly digitalized, but the course continued to be downhill, and the baby expired on the third hospital day.

From the results presented we feel that the flush method is a reasonably accurate and simple means of deter-

mining the approximate systolic pressure in normal newborn infants and in infants with the abnormalities cited previously. Since newborn infants have a higher hemoglobin content, the end point or the appearance of the flush is distinct and compares favorably with established blood pressure findings as reported by Woodbury, Robinow, and Hamilton.[1] It would be of interest to be able to establish criteria for diagnosis of coaretation of the aorta in newborn infants, but at present we have insufficient data to set forth a reliable gradient between the pressure of the upper and lower extremities. From the few studies we have made it would seem that a gradient greater than 20 mm. Hg between the upper and lower extremities may be enough to warrant a diagnosis of coaretation in a suspected case.

SUMMARY

A visual method of determination of blood pressures in newborn infants is presented. The cuff is placed around the ankle or wrist in the usual manner and a piece of rubber sheeting or old rubber glove is wrapped snugly around the foot or hand, so that the blood is pressed from the extremity. The cuff is then inflated to a pressure slightly above the suspected systolic pressure, the rubber bandage is then removed and the pressure is slowly released from the cuff. The approximate systolic pressure is the reading at which blood suddenly re-enters the foot or hand, causing a flush.

We wish to thank Dr. A. F. Hartmann and Dr. J. V. Cooke for their valuable guidance and criticism during the preparation of this work.

We wish to thank Dr. Bernard Schwartzman for permission to use his case R. D. in this study (Table IV) and to thank Dr. Herbert Mazur for permission to use his case L. H. (Table III).

We wish to thank Dr. Arnold Schuman for the preparation of the diagram used in this report.

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A CLINICAL REPORT ON AMEBIASIS IN INFANTS UNDER ONE YEAR OF AGE

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INTRODUCTION

ALTHOUGH amebiasis in adults is now recognized as a not uncommon disease in the United States, this infection in infants, particularly under one year of age, is thought to be relatively rare. Craig[1] states that the majority of amebic infections occur in patients over 20 years of age, and that the paucity of cases in infants is due to insufficient exposure. In the United States, Craig[1] and Faust and Headlee[2] report an incidence of 0.8 to 0.9 per cent in infants under one year of age, while in Europe, Manson-Bahr[3] reports an incidence of 0.9 per cent in all children under 10 years of age. In the Chicago area, Howell and Knoll[4] recorded a percentage of 3.18 in infants and children. Shrapnel and associates[5] in Panama, and De Silva[6] in India have quoted even higher figures (Table I).

The protean manifestations of amebiasis in adults are well known.[1, 3, 7] However, the clinical picture of this disease in infants is relatively unknown.[8, 9, 10] Our study of amebiasis was prompted by the large number of "problem" cases of gastrointestinal dysfunction in infants encountered at the Children's Division of the Cook County Hospital. In spite of the fact that amebiasis is not always considered in the differential diagnosis during infancy, our cases of gastrointestinal disturbances of unknown etiology were subjected to protozoologic studies, and many were found to harbor amebas. At the end of one year (July, 1949, to July, 1950), eighty infants with amebiasis were found among 872 cases of diarrhea in infants and children, an incidence of 9.2 per cent.

LABORATORY DIAGNOSIS

The diagnosis of amebiasis must be established by laboratory methods. Thus, only such cases were considered as amebic in which the stool examination demonstrated the presence of *Endamoeba histolytica*. The stool was examined by the parasitology department in the following manner:

Only stools which were brought to the laboratory within one-half hour after being passed were examined. This assured the study of a fresh specimen in each case.

The gross appearance and consistency of the stool, as well as the presence of gross blood, or mucus was noted.

One smear of the stool in physiologic saline, and another smear using D'Antoni's[11] iodine method were immediately examined microscopically for the presence of active trophozoites.

Permanent hematoxylin-stained mounts were prepared immediately using the freshly passed stool. These slides have the advantage of easier nuclear differentiation of the protozoa. Young and collaborators[12] in a recent

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Read before Chicago Pediatric Society Meeting, April, 1951, Chicago, Ill.

Awarded the third annual Maurice Lamm Blatt prize.

study found 91 per cent of the positive cases by this method alone, whereas the saline and iodine methods had disclosed only 28 per cent of the cases.

In the present study, the protozoa was found within the first three stool specimens collected in 90 per cent of the infants. Table II illustrates that in three suspicious cases, as many as six specimens were examined before the ameba could be found. Craig[1] has clearly pointed out that frequently several stool examinations are necesary to make the diagnosis, and that the percentage of positive stools increases with the number of stool examinations performed.

Table I. Incidence of Childhood Studies of Amebiasis

Author	Location	Age	Positive Cases	
			Number	Per Cent
Craig	Rural	0-5 yr.	—	0.9
Manson-Bahr	Europe	Below 10 yr.	257	0.9
Shrapnel, Johnson, and Sandground	Panama	—	20	10.0
De Silva	India	0-2 yr.	40	15.9
Taubenhaus	N. Carolina	0-10 yr.	3	7.6
Howell	Chicago	8 mo. to 13 yr.	13	3.18
Faust and Headlee	New Orleans	0-1 yr.	116	0.86

Table II

	Positive for E. histolytica						
	1st stool	2nd stool	3rd stool	4th stool	5th stool	6th stool	Total
Number of Cases	41	19	12	4	1	3	80
Per cent of Cases	51.3	23.7	15	5	1.2	3.8	100%

Bacterial stool cultures were obtained before and after treatment, and bacterial diarrhea was sharply distinguished from amebiasis.

The complement fixation test for amebiasis was not carried out on our patients.

Proctoscopic Findings

The proctoscopic picture of amebic colitis in adults has been adequately described.[1, 3, 13] The classic description is that of patchy areas of inflammation, consisting of multiple petechial hemorrhages, nodules, and undermining ulcers with a necrotic base. However, there is little in the literature concerning proctoscopic findings in amebiasis in infants. Thus, we hoped that proctoscopy might prove to be a valuable corollary to the diagnosis, and perhaps also help in evaluating the efficacy of treatment.

The infant to be proctoscoped was prepared with a small saline enema the morning of the examination. Oral feedings were withheld following the enema, and the infant was examined three hours later. No sedation was required in this age group. The infant was placed prone on a small table, and the thighs and legs allowed to hang over the edge of the table. A digital examination was done which served to rule out adhesive bands, rectal polyps, and strictures. At the same time, the rectal sphincters were dilated. After this a $\frac{5}{16}$ inch diameter, 6½ inch long proctoscope, with proximal illumination, was introduced and passed under direct vision.

Seventy-seven of the eighty infants with amebiasis were proctoscoped and the findings are listed in Table III.

Of these 77 infants, five showed no abnormality; the mucosa was pink and intact.

Twelve patients demonstrated some hyperemia of the mucosa with an excess of mucus. A few areas of granular patches were seen which were considered an infectious response of the mucosa.

Twenty infants had multiple petechial hemorrhages surrounded by normal mucosa. A pinhead-sized ulcer was seen in the center of some petechia. No typical large ulcer, with a necrotic base, was found.

Forty patients had clusters of discrete, multiple, petechial hemorrhages, without ulcers.

Nodules, which are common, and pathognomonic in adults, were not seen in any of the proctoscoped infants. No correlation between the proctoscopic findings and the clinical symptoms could be drawn, since 78.2 per cent of all of the patients proctoscoped had petechial hemorrhages. The presence of petechial hemorrhages evoked our suspicion of amebic infection, even when two or more negative stools had been reported. In these instances, repeated stool examinations did reveal *E. histolytica*, although in three cases as many as six stools were required before the organism could be identified.

Proctoscopy was useful in determining the progress and prognosis of the antiamebic treatment. For example, there were seven patients with pathologic findings on proctoscopy in each of whom the symptoms of diarrhea ceased on specific antiamebic therapy. In each of these seven patients, however, rectal lesions persisted after therapy, and a relapse soon occurred. Later, in such instances, antiamebic therapy was continued beyond our arbitrary time limit until the rectal lesions subsided, whereafter no relapses occurred. However, it is not advisable to substitute proctoscopy for the parasitologic examination of the stool. The procedure has its limitations, but it is extremely useful as an adjunct, and corollary to the diagnosis and treatment of amebiasis.

TABLE III. DISTRIBUTION OF PROCTOSCOPIC FINDINGS IN SEVENTY-SEVEN CASES OF AMEBIASIS

CASES PROCTOSCOPED		
NO. CASES	% CASES	APPEARANCE OF INTESTINE
5	6.23	No abnormality. The mucosa was pink and intact.
12	15.58	Hyperemia of the mucosa Excess mucus Granular patches
20	26.24	Clusters of multiple petechial hemorrhages with central pinhead-sized ulcer. Hemorrhagic area surrounded by normal mucosa.
40	51.95	Multiple petechial hemorrhages Each area discrete No ulcers noted No nodules

CLASSIFICATION OF THE CLINICAL PICTURE OF AMEBIASIS

D'Antoni and Sodeman[14] have described a hepatoneurotic syndrome occurring in infants and children with amebiasis. They found a rather characteristic clinical picture consisting of a muddy complexion with marked ir-

ritability, usually associated with a low-grade fever, and a palpable, tender liver. Slight constipation was the rule, although mild diarrhea did occur in some instances.

Upon analysis of the clinical history and course of the disease, our eighty patients could be divided into four main groups (Table IV).

However, stools obtained on the second and fifth days of hospitalization contained *E. histolytica*. During that time only one abnormally loose stool with excess mucus was passed. Proctoscopy revealed an occasional patch of petechial hemorrhages.

Antiamebic therapy was instituted and consisted of iodinized bactiracin, 10,000 units per day for fourteen days.

TABLE IV. CLASSIFICATION OF CLINICAL GROUPS OF EIGHTY INFANTS UNDER 1 YEAR OF AGE

GROUP	NO. OF CASES	PER CENT CASES	CLINICAL FINDINGS
I	15	17.8	Occasional loose stool alternate with normal stool or obstipation. Mucus in occasional stool.
II	50	62.50	Severe dehydration. Mild or marked pallor and anemia. Profuse watery stools. 8 or more stools per day. Mucus or blood may or may not be present.
III	8	10.0	Intermittent spiking fever 100-103° F., slight enlargement of liver. Early diarrhea or obstipation. Mild leukocytosis.
IV	7	9.7	Marked abdominal distention. Much foul flatus. Malnutrition—poor fat reserves. Stools bulky, large, light colored, curdy—often no diarrhea.

Group I was composed of 15 infants who had an occasional loose stool, with alternate normal bowel movements or obstipation. Occasional mucus in the stool was found.

CASE 1.—This 2-month-old Mexican female entered the hospital on Dec. 13, 1949, with acute otitis media, and a severe upper respiratory infection. A history was obtained of an occasional loose stool with mucus since one month of age.

Physical examination revealed a well-developed female infant weighing 8 pounds, 6 ounces, with a rectal temperature of 101° F. Examination was negative except for catarrhal otitis media and rhinitis.

During the first six hospital days, procaine penicillin, 150,000 units per day, was given, and the ear infection and rhinitis improved.

During this therapy, there were no loose stools with mucus.

Three stools obtained at forty-eight-hour intervals after treatment were negative. They remained negative three months after the patient was discharged from the hospital.

Repeated bacterial stool cultures for Salmonellae and Shigellae were consistently negative before and after therapy.

Group II consisted of fifty infants, all of whom entered the hospital acutely ill, very toxic, and with extreme dehydration and acidosis. These patients had profuse, almost continuous, watery stools. However, gross blood was present in only five instances, and was not profuse. Many in this group presented a marked pallor, and required blood transfusions

in addition to parenteral fluid management to maintain life.

CASE 2.—This 3-month-old white male was admitted to the hospital on Nov. 6, 1949, with a one-week history of three to four loose, green stools per day. The stools were becoming progressively more profuse.

Physical examination revealed a markedly dehydrated, toxic, malnourished infant who weighed 9 pounds, 1 ounce. The rectal temperature was 99° F., and the remainder of the examination was noncontributory.

On the fourth hospital day, *E. histolytica* was found in the stool. The bacterial stool culture was negative for Salmonellae and Shigellae.

Antiamebic therapy consisting of iodinized bacitracin was started on November 10.

On the thirteenth day of therapy, the infant had two explosive, watery stools, and went into collapse. Immediate intravenous fluids, followed by a blood transfusion, saved the patient's life.

On the fourteenth day of iodinized bacitracin therapy, *E. histolytica* was again found in the stool.

Because of the severe, profuse nature of the stools, we decided to give emetine hydrochloride, $\frac{1}{20}$ grain per day, and observed the patient closely. After only three days of emetine treatment, the stools returned to normal, but the drug was continued for an additional two days.

On the twenty-fifth hospital day, Milibis, 50 mg. per kilogram of body weight, was started for the next fourteen days. No relapse occurred. The infant now weighed 9 pounds 14 ounces.

Three stools were negative for *E. histolytica* after the twenty-fifth day.

The patient was hospitalized two additional months because of malnutrition and he remained free of amebas. No relapse occurred.

Group III consisted of eight infants with intermittent fever, which was not explained by physical or laboratory diagnosis. Diarrhea or obstipation was present. The liver was slightly enlarged, but liver function tests remained normal. When antiamebic therapy was started, these patients became afebrile, the enlarged liver regressed to normal, and the infants began to gain weight.

CASE 3.—This 8-month-old Negro female was admitted to the hospital on Nov. 1, 1949, with a history of several loose, green stools daily for five days. Three days prior to admission, the patient began to vomit two to three times per day.

Physical examination revealed a well-developed Negro female who appeared listless. The rectal temperature was 102° F. No abdominal distention was present, but the liver was palpable 3 cm. below the right costal margin.

During the first nine hospital days, the infant was treated with procaine penicillin, 300,000 units daily, sulfadiazine, 2 grains every four hours, and parenteral fluids. The diarrhea continued without improvement.

On the tenth hospital day, *E. histolytica* was reported in the stool. Proctoscopy revealed hemorrhagic petechiae in the center of which a pinhead-sized ulcer could be seen.

Diodoquin, 2 grains per kilogram of body weight, was administered for fourteen days. In addition, Aralen, 50 mg. per kilogram of body weight, was administered orally. The patient was afebrile three days after this therapy was started and the liver's edge could barely be palapted below the right costal margin. Parenteral fluids were discontinued after seven days and the stools remained normal after the eighth day.

Liver function tests remained normal. Proctoscopy was negative at the end of the treatment.

Group IV consisted of seven infants, each of whom presented a syndrome resembling celiac disease. These infants had marked abdominal distention and produced much foul flatus.

They were chronically ill, had failed to do well prior to admission, were not gaining weight, and were poorly developed. The stools were bulky, large, and light colored. Diarrhea was not constant and was variable from day to day. Trypsin was demonstrated in the stools; vitamin A absorption and glucose tolerance tests were normal. After antiamebic therapy was started the sprue syndrome rapidly disappeared.

gradually reduced to normal, and on the last day of treatment, the infant was gaining weight for the first time. After treatment, proctoscopy revealed a pink and intact intestinal mucosa, and three stools were negative for *E. histolytica*. The infant was discharged on Dec. 18, 1949, weighing 8 pounds 14 ounces. The stool was free from amebas three months later.

In this series, chronic malnutrition and transient hepatitis were the only complications found.

TABLE V. COMPARISON OF SPECIFIC ANTIAMEBIC TREATMENT GIVEN TO EIGHTY INFANTS WITH AMEBIASIS

	PATIENTS TREATED		CLINICALLY IMPROVED		STOOLS NEGATIVE AFTER TREATMENT		STOOLS NEGATIVE AFTER 3 MO.	
DRUG TESTED	NO.	%	NO.	%	NO.	%	NO.	%
Baitracin Iodized	25	31.25	17	64	11	44	7	28.0
Bacitracin	30	37.50	27	90	21	70	16	53.4
Diodoquin	25	31.25	19	76	17	68	13	52.0
Total	80	100	63	78.75	49	61.25	36	45.0

CASE 4.—This 2-month-old white male entered the hospital on Nov. 16, 1949, with a history of intermittent diarrhea since birth. He had been studied at another hospital for possible celiac disease or fibrocystic disease of the pancreas because of the intermittent diarrhea, abdominal distention, and failure to gain weight.

Physical examination revealed a pale, dehydrated infant, who had prominent features of malnutrition with exhaustion of the fat reserves. The temperature was 99° F. rectally, and the infant weighed 7 pounds 2 ounces on admission.

On November 17, *E. histolytica* was reported in the stool. Proctoscopy revealed an edematous mucosa, with much mucus and many petechial hemorrhages. Two bacterial stool cultures were negative for pathogenic organisms. Trypsin was present in several stools. The vitamin A absorption curve was normal.

Bacitracin, 10,000 units per day, was given orally for fourteen days. Within the first three days, the stools became normal and the dehydration improved. The distended abdomen

One has to add that no extra-intestinal abscess formation was observed and no instance of intestinal perforation occurred. There were no deaths among the eighty infants with amebiasis.

SPECIFIC THERAPY

The discussion of treatment will be limited to specific antiamebic drugs, although supportive measures were of paramount importance in the management of many of the infants (Table V).

1. A series of twenty-five cases was given oral bacitracin. Each tablet contained 10,000 units of bacitracin. Infants under 7 kilograms were given 10,000 units per day for fourteen days. Those over 7 kilograms were given 20,000 units for the same period of time.

Seventeen infants (64 per cent) improved clinically during this therapy.

Eleven patients (44 per cent) were free from amebas immediately after therapy, but only seven (28 per cent) of these patients had negative stools at the end of three months.

Bacitracin was well tolerated in the dosages used, and no toxic effects were noted at any time during treatment.

2. A series of thirty patients was given iodinized bacitracin, made by Commercial Solvents Corporation. Each tablet contained 10,000 units of bacitracin with 12.5 per cent iodine, in the hope that the latter would improve the efficacy of this antibiotic. The dosage was the same as for pure bacitracin.

Twenty-seven infants (90 per cent) improved clinically during this treatment.

Twenty-one patients (70 per cent) were free from amebas immediately after therapy, but only sixteen infants (53.4 per cent) were still negative at the end of three months.

Iodinized bacitracin was well tolerated and no toxic effects were encountered.

3. A series of twenty-five infants was given Diodoquin. Each tablet contained 3.2 grains of the drug. The dosage was 2 grains per kilogram body weight per day for fourteen days.

Nineteen infants (76 per cent) showed clinical improvement during treatment.

Seventeen patients (68 per cent) were free from amebas immediately after therapy, but only thirteen of these infants (52 per cent) were still negative at the end of three months.

Diodoquin was well tolerated, and no toxic effects were encountered.

Altogether, eighty infants under one year of age were treated for amebiasis. At the end of fourteen days of therapy, forty-nine patients (61.25 per cent of all the cases) had negative stools. Only thirty-six of the eighty infants (45 per cent) remained negative three months after discharge from the hospital.

It is difficult to determine whether our high failure rate after the patients returned to their homes was due to ineffectiveness of the therapy, relapse or to reinfection.

Shlaes and associates[15] examined the stools of 125 families of patients with amebiasis and found that in 88 per cent of the families, in addition to the patient, at least one other member harbored amebas. Thus, it was possible that a recurrence of the disease was due to reinfection from another member of the family.

Relapses and resistant cases were treated with one or more of the following drugs: emetine hydrochloride, Milibis, Vioform, Aralen, or a second course of bacitracin or Diodoquin.

The various forms of therapy used afforded clinical improvement. However, the results of follow-up stool examinations show that the treatment of amebiasis in infants is still not too effective.

DISCUSSION

The diagnosis of amebiasis in eighty infants in this hospital emphasizes the importance of competent parasitologic study in the evaluation of infantile diarrhea, in addition to stool culture methods for pathogenic bacteria.

Of highest clinical significance, in our series, were those cases of severe diarrhea which failed to respond to routine management. After several days, *E. histolytica* was observed in the stools of these patients, and prompt clinical response occurred after specific therapy was instituted. The diarrhea stopped within three to four days, hydration was restored to

normal, and parenteral fluids could be discontinued.

Of equal significance, but less common, was the group of infants who presented a celiac-like syndrome, consisting of abdominal distention and malnutrition, with exhaustion of the fat reserves. Intensive laboratory investigation, which included oral glucose tolerance and vitamin A absorption tests, tryptic digestion of x-ray film, and blood chemical tests, failed to establish the diagnosis of celiac or pancreatic disease. After *E. histolytica* was found, these patients were given antiamebic therapy, with rather prompt improvement of the condition.

Our study also demonstrated the importance of proctoscopy in the diagnosis and in the evaluation of antiamebic therapy.

Suspicious proctoscopic findings, such as petechial hemorrhages, were often the clue to the diagnosis and prompted us to have repeated stools submitted to the laboratory for parasitologic study.

Treatment consisted of bacitracin, iodinized bacitracin, or Diodoquin. Iodinized bacitracin and Diodoquin were the most effective. All drugs produced a favorable clinical improvement. However, during a three-month period following treatment, 55 per cent of the patients had a recurrence of *E. histolytica* in their stools.

The low cure rate indicates the need for better specific antiamebic drugs and hygienic measures. Treatment of other infected members of the family may influence the permanent cure rate.

SUMMARY

1. Eighty cases of amebiasis in infants under one year of age were studied.

2. The importance of repeated stool examinations is emphasized.

3. Proctoscopy of infants was found to be an invaluable procedure for evaluating gastrointestinal diseases encountered in this age group.

4. Four clinical types of infantile amebiasis were described.

5. The treatment was briefly discussed.

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EVALUATION OF "SETON" PROCEDURE IN THE TREATMENT OF INFANTILE COMMUNICATING HYDROCEPHALUS

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IN 1933 Hiller[1] described a simple procedure for the treatment of communicating hydrocephalus in infants. The procedure consists of inserting a silk thread through a specially designed spinal puncture needle into the lumbar subarachnoid space. The needle is then withdrawn and the thread is cut off so that its end lies just below the level of the skin. A tract is thus established for the flow of cerebrospinal fluid from the caudal sac into the adjacent soft tissues (Fig. 1).[2]

The simplicity and safety of this method, which requires only local anesthesia, appealed to us, and we have employed it in twenty-four cases in which, for one reason or another, major surgical procedures were not advised. In fifteen of these cases, this procedure failed to alter the inexorable advancement of the hydrocephalic process. In nine patients so treated, however, it appears to us that the hydrocephalic process has been arrested.

In seven cases, the increment in the size of the head after the procedure was within or was less than the expected normal increment. The expected normal increment in each case has been derived from the tables showing normal growth prepared by Watson and Lowrey.[3] In two other cases the disease was considered to be arrested because, even though the increment in head size exceeded the expected normal, in each case the head continued to grow at an accelerated rate for some months after the procedure, but finally reached a point at which the size remained stationary (Cases 8 and 9). The children are at present, respectively, 5½ and 6½ years old.

Brief reports of these nine cases follow:

CASE REPORTS

CASE 1.—The seton procedure was carried out March 5, 1947, on a baby girl 5 months of age. The head increased in circumference from 49.5 cm. on admission to 59.9 cm. on Oct. 9, 1950, an increase of 10.4 cm. in forty-three months. The expected increase was 8.3 cm. (standard deviation, S.D., 1.2 cm.). The family physician's evaluation of the patient stated, "Child has very high I.Q. She seems to have the intelligence of a 6- or 7-year-old child. Fairly marked spasticity of the lower extremities but she walks well with an orthopedic walker."

CASE 2.—The seton procedure was carried out on Nov. 19, 1945, on a baby girl, 7 months of age. There was an increase in the size of the head from 52.5 cm. on admission to 59.2 cm. on Nov. 6, 1950. This was an increase of 6.7 cm. in sixty months. The normally expected increase was 7.1 cm. (S.D. 1.4) (Fig. 2). Her home physician wrote, "The child is alert and well behaved. She is on a full program of

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academic work and occupational therapy. She has some weakness of the left hand, but with training the hand is becoming more useful. We feel she has good potentialities."

CASE 3.—A girl, 6 months of age, underwent the seton procedure on March 16, 1945. The size of the head increased from 52 cm. on the patient's admission to 60 cm. in November, 1950, an increase of 8 cm. in sixty-eight months. The normally expected increase was 7.8 cm. (S.D. 1.4). A letter from the patient's mother and the home physician in November, 1950, stated that the patient's I.Q. was normal. She was walking well with braces. Her vision was normal although she had a slight left rectus squint (Fig. 3).

CASE 4.—The seton procedure was carried out on an 8-month-old boy, March 28, 1947. The head increased in size from 55.8 cm. on his admission to 60.9 cm. on July 20, 1950, an increase of 5.1 cm. in forty-one months. The normally expected increase was 6.1 cm. (S.D. 1.2). The family physician wrote in July, 1950, that the patient talked well, seemed bright, could count to 10 and had memorized nursery rhymes. He was able to feed himself, could sit up on the floor, but could not walk.

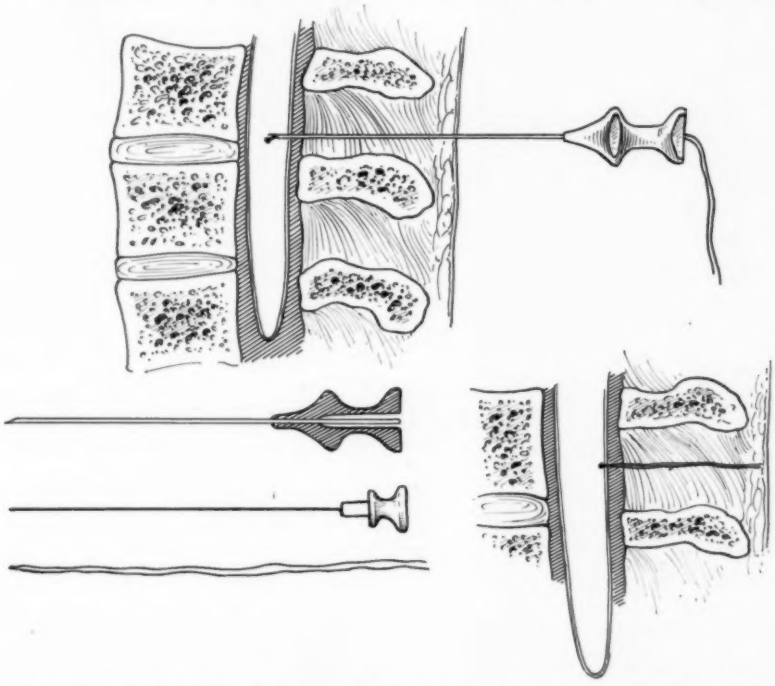

Fig. 1.—Seton spinal needle with stylet and knotted silk string; note method of insertion into lumbar subarachnoid space and into the subcutaneous tissues.

CASE 5.—A baby girl, 6 months of age, underwent the seton procedure on July 9, 1949. Subsequently the head increased in size from 53.7 cm. on her admission to 56.5 cm. on July 18, 1950. This was an increase of 2.8 cm. in twelve months. The normally expected increase was 5.0 cm. (S.D. 1.2). A recent letter from the parents stated that the child seemed all right men-

Fig. 2.

Fig. 3.

Fig. 2.—Patient in Case 2 (October, 1950) at age of 5 years.

Fig. 3.—Patient in Case 3 (June, 1950) at age of 5 years.

Fig. 4.—July, 1950; patient about 1½ years of age (Case 5).

Fig. 5.—Patient (Case 6) in March, 1950. The child was almost 3 years of age.

Fig. 4.

Fig. 5.

tally, but that she had the physical ability of a child only 8 or 9 months of age (Fig. 4).

CASE 6.—On Nov. 7, 1947, the seton procedure was performed on a baby girl 2½ months of age. The head increased in size subsequently from 39 cm. to 54.3 cm. on July 11, 1950, an increase of 15.3 cm. in thirty-three months. The expected increase in size was 10.0 cm. (S.D. 1.2). The family physician wrote that the patient's mental ability was good, and that she was alert, talked well and in general her health was good (Fig. 5).

CASE 7.—The seton procedure was carried out on a boy, 8 months of age, on Jan. 29, 1948. Subsequently the head increased in size from 47 cm. to 51.4 cm. on Sept. 11, 1950. This was an increase of 4.4 cm. in thirty-one months during which time the normally expected increase was 5.7 cm. (S.D. 1.2). The home physician wrote on September 11 that the boy had regained some eyesight and ate well but seemed to have a low I. Q.

CASE 8.—The seton procedure was carried out June 24, 1944, on a baby boy 6 months of age, after which the head increased in size from 49.5 cm. to 62 cm. in July, 1950. This represented an increase of 12.5 cm. in seventy-three months. The expected increase in size was 7.8 cm. (S.D. 1.4). A letter from the parents in July, 1950, stated, "The child is somewhat rigid and spastic and has only light perception but his hearing is good. There has been no further head growth as far as we can tell since November, 1944."

CASE 9.—An 11-month-old boy underwent the seton procedure on Oct. 19, 1945. After the operation the head increased in size from 54 cm. on his admission to 66 cm. on June 2, 1950, which represented an increase of 12 cm. in fifty-six months. The normally expected increase is 5.4 cm. (S. D. 1.4). The parents wrote in June, 1951, that there had been no further increase in the size of the head. In so far as they could determine they felt that the child had a normal I. Q. He was of school age and would enter in the fall. Although he had a slight handicap in the right hand and leg, he was able to walk fairly well (Fig. 6).

Fig. 6.—Child nearly 6 years of age (Case 9) (June, 1950).

EVALUATION OF RESULTS

The success or failure of any procedure designed for the treatment of communicating hydrocephalus can be gauged fairly by just one criterion; namely, the control of the size of the head.

Whatever the anomalies or defects of the central nervous system associated with the hydrocephalus, they are unaffected by procedures designed to arrest the hydrocephalic process. Thus, in some instances, although the size of

the head is successfully controlled, mental deficiency, convulsive disorders, spasticity, and various other signs and symptoms may persist and thus to some extent vitiate the results of treatment.

Fortunately, however, in some cases, if the hydrocephalic process can be arrested before irreversible damage to the brain occurs, a relatively normal mentality and physical development without the stigmas mentioned previously can be hoped for.

An occasional case of spontaneous arrest of communicating hydrocephalus is sporadically encountered, in which the only stigma remaining is the enlarged head. The incidence of such spontaneous arrest in cases of severe hydrocephalus is not known but certainly it is not high. Ford[4] has stated that hydrocephalus developing shortly after birth and progressing rapidly is usually fatal before the end of the first year. Most authors agree that only occasionally does a severely hydrocephalic child reach the age of 7 years.[5]

Although the results in the cases reported are not striking, we are of the opinion that they represent considerably more than the spontaneous remission rate would account for.

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HEREDITARY ECTODERMAL DYSPLASIA OF THE ANHIDROTIC TYPE

Report of a Case in a Negro

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ANHIDROTIC hereditary ectodermal dysplasia is a condition involving mainly, but not exclusively, many structures derived from ectoderm with evidence of fundamental developmental changes in these structures. The condition was first identified in 1920 by Goeckermann[1] who called it a major or high-grade ectodermal defect to distinguish it from the multitude of variable cases reported with only one or two ectodermal structures involved. Weech[2] in 1929 introduced the now more widely accepted term of hereditary ectodermal dysplasia of the anhidrotic type which describes the condition more accurately and distinguishes it from a more common hidrotic form.

While the earliest case report of the anhidrotic type is generally attributed to Widderburn in 1838,[7] and the earliest American cases are thought to be those of Guilford or Atkinson[8] in 1882, it is of some significance that probably less than 100 true cases have been reported to date. In addition, while cases have been described in natives of India and Ceylon,[7, 9] so far as we could ascertain, only one certain case has been described in a person with Negro blood. In 1937 Cappir and Bekir[10] reported a 6-year-old mulatto girl of Armenian and Irish descent with practically white skin who never perspired, developed lacrimation at the age of 4, had only one tooth, had atrophic rhinitis, lack of definition at the vermillion border of the lip, and low blood sugar curve.

The anhidrotic type, an example of which we are presenting, must be distinguished from a more common hidrotic form of ectodermal dysplasia in which there is no apparent alteration of perspiration. This latter type is found in many members of a family, both male and female, and is apparently inherited through nonsex-linked dominant genes, never skipping but decreasing in severity with each generation.[6] While they resemble the anhidrotic type clinically in hair and tooth pathology, they differ in that they lack nose or throat symptoms and usually have nail deformities. In addition, the basal metabolic rate may be low and the glucose tolerance curve high in the hidrotic form, but the reverse is usually found in the anhidrotic type.[6]

The identifying features of this syndrome are: (1) heat intolerance due to a generalized absence of the sweat gland apparatus; (2) partial to complete absence of both deciduous and permanent teeth with deformity of those which are present; (3) a decreased number of hair follicles and sebaceous glands evidenced by a dry, smooth, shiny skin; papillary lesions on the face (degenerated sebaceous glands with surrounding acanthosis[3]); absent or sparse eyelashes and eyebrows; and sparse, fine dry hair.

Other disturbances more or less commonly found in these patients are: atrophic rhinitis, chronic pharyngitis

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and laryngitis, absent taste and smell, deformed ears, such as absent lobules or satyr shape, conjunctivitis, absent tears, apparent saddling of the nasal dorsum, absent mammary glands, adrenal insufficiency,[4] everted lips with poor definition of the vermillion margin, and thickened cranial bones.[5]

The hereditary factor is appropriately included in the name because, once started, the pathology appears to be transmitted by a sex-linked recessive gene passed by the female to male offspring.[2] Clinically, this is evidenced by its appearance mostly in males and frequently, but not necessarily, in only one member of each generation.

We are reporting this condition in a boy of mixed Negro, Irish, and Scotch descent. While it is probable that these characteristics were inherited from one of his white maternal great-grandparents, according to our review, this appears to be the second Negro case to be reported in the English literature.

CASE REPORT

A 26-month-old Negro boy (J.R.N.) was admitted to Los Angeles Childrens Hospital on Sept. 20, 1949, for treatment of acute tonsillopharyngitis with marked cervical adenitis. His mother stated that the patient had evidenced heat intolerance since birth. Often, when hot, he would voluntarily remove all his clothes and lie down in the shade, an action which he pursued in spite of repeated reprimands. He had never been observed to perspire.

The mother bled during the first month of pregnancy at which time she was confined to bed. There was "decreased vision" during the second trimester unassociated with rise in blood pressure or swelling of the lower extremities. These troubles disappeared before delivery. There was no known infectious disease during pregnancy. Birth was normal, spontaneous, full term, and not prolonged.

General development was apparently normal. Patient sat up at 6 months and walked at 11 months, but at no time had the mother observed eruption of teeth.

Patient was of full Negro ancestry except for two white maternal great-grandmothers, one of whom was Irish, and one of whom was Scotch. One of these was stated to have had sparse hair and some intolerance to heat with frequent syncope. The rest of the family history was negative for abnormalities of ectodermal structures.

There is one sibling aged 4 years, a sister, with mongolism and no evidence of ectodermal dysplasia.

The patient was a small but well-nourished Negro child who was alert, yet shy and withdrawn. His skin was dry, dark, and shiny throughout. This was especially so over the face where many papules were visible over the nose and cheeks. There were areas of deeper pigmentation over the nose and forehead. The palms, soles, and axillae were dry. The hair of the head was fine, dry, and sparse but fairly evenly distributed. There were no visible eyebrows, axillary or pubic hair. The eyelashes were apparently normal, as were the nail and nipples.

With crying, there was good lacrimation bilaterally. The conjunctivae were clear. The lids were not wrinkled. Funduscopic examination was negative except for some myopia.

The aurieles had poorly developed but definite lobules. There was a small amount of brown dry cerumen in each canal. There were also fine hairs in the outer portions of each canal. The hearing was apparently normal.

The nasal dorsum was flat and broad. This was thought to be due to the presence of small flattened nasal bones without any arch formed at their common suture site. The nasal processes of the maxillae were easily palpated slightly lateral to the lateral margins of the nasal bones. The flattening of the nasal dorsum appeared to be accentuated by rather prominent supra-

Fig. 1.

Fig. 2.

Fig. 1.—Patient J. R. N. without dentures. Note the flattened nose and abnormally smooth, shiny skin.

Fig. 2.—Same patient with dentures. The almost complete absence of eyebrows is well shown.

Fig. 3.—Roentgenogram of maxilla and mandible, showing complete absence of tooth buds.

orbital ridges. Both nasal airways were filled with thick, dry, greenish crusts and casts and the underlying mucosa was reddened, thin, and dry. The sense of smell appeared to be intact. The upper lip was slightly prominent while the lower lip was greatly everted causing some deformity. The lip margins were definite. The tonsils were large and infected with much anterior and posterior cervical adenopathy. The voice was slightly raspy but not hoarse. There were no teeth visible in either arch.

cent (normal 5 to 7); blood calcium, 7.3 and 10.8 mg. per cent; serum inorganic phosphate, 516 mg. per cent; fasting blood sugar, 55 mg. per cent. Glucose tolerance curve (June 15, 1950): Fasting blood sugar 90, after 30 minutes, 130; 60 minutes, 182; 120 minutes, 174; 180 minutes, 99. There was no sugar in the urine at any time during the test. Nasal culture: Beta hemolytic streptococcus, diphtheroids, and hemolytic *Staphylococcus aureus*. coagulase were positive. X-rays: Bone age at wrist was normal for age.

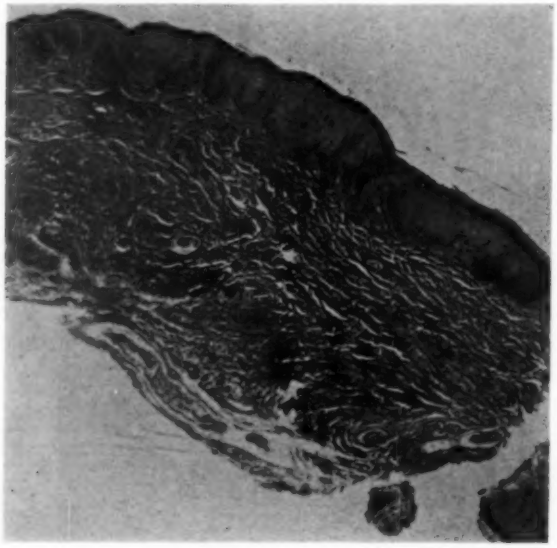

Fig. 4.—Histopathological section of skin from axilla, showing complete absence of sweat glands.

Neurological examination was negative. Psychological tests revealed "significantly better than average intelligence." Nasopharyngeal examination, direct laryngoscopy and bronchoscopy, all under general anesthesia, failed to reveal any pathology. Urinalysis, complete blood count including bleeding and clotting times and platelet counts were all normal. Wassermann and Mantoux tests were negative.

Other laboratory findings were as follows: blood iodine, 4.6 and 5.8 μg per

Skull film was negative. Maxilla and mandible showed no evidence of dentition or tooth buds.

Biopsies were examined by Dr. Ralph Knutti.

From right axilla: "Specimen shows one margin lined with thin stratified squamous epithelium with normal-appearing rete pegs. The corium is of normal thickness. Two hair follicles are noted and in one area there is a small portion of a sebaceous gland. No sweat glands are noted."

From junction of squamous nasal vestibule and membranous septum: "Specimen shows no glands."

SWEATING TEST

1. The patient and a hospital control, a child with congenital esophageal stenosis who had received dilatations and was asymptomatic, were placed on adjoining beds in a room with a temperature of 76° F. and humidity of 52 per cent. Both were covered with Minors* iodine solution and then starch over the face, neck, anterior chest, abdomen, groin, axillae, arms, and legs. To facilitate sweating, each patient was exposed unclad to two 100-watt lights with one approximately eighteen inches away from the head and one the same distance from the chest. During the procedure two investigators watched both patients. A hand magnifying glass was used to facilitate detection of early changes. Under these conditions the temperature in the patient with ectodermal dysplasia rose from 100.0° F. rectally to 102.3° F. rectally in seventy-three minutes, but at no time during the procedure was perspiration observed anywhere on his body. The control patient, however, showed perspiration in the axilla at twelve minutes and perspired generally by twenty-three minutes with no significant rise in temperature being observed during this period. (See Table I.)

2. When the temperature returned to 100° F. rectally, the patient was given 1.25 mg. of Mecholyl subcutaneously (0.05 mg. per pound of body weight). He was then observed by the iodine-starch method for another thirty minutes without apparent perspiration.

3. Five hundred cubic centimeters of milk at approximately 110° F. were given to the patient and his control. Following this, rectal temperatures were taken. That of the control did not rise at all while that of the patient was elevated one full degree in twenty minutes.

TABLE I. RESPONSE TO EXTERNAL HEAT

TIME MINUTES	RECTAL TEMPERATURE		OBSERVATIONS		HEAT APPLIED	
	PATIENT	CONTROL	PATIENT	CONTROL	PATIENT	CONTROL
12	100.0	100.0	No change	Perspiration in axilla	Yes	Yes
18	100.1	100.0	No change	Perspiration on face and chin	Yes	Yes
23	100.2	100.1	No change	Perspiration on thighs, chest, forehead	Yes	Yes
38	100.3		No change		Yes	Discontinued
53	101.2		Restless. No perspiration		Yes	
68	102.0		Crying. Restless		Yes	
73	102.3		Very uncomfortable. No perspiration		Yes	
92	100.4				Discontinued	
102	100.3					

DISCUSSION

This case appears to be a typical example of anhidrotic ectodermal dysplasia. The family history is quite in-

*Minors iodine solution contains iodine 4 Gm. castor oil 20 c.c. and absolute alcohol 180 c.c. This with the starch will produce a change from white to purple in the presence of perspiration.

teresting in view of the white maternal great-grandmother who reputedly had sparse hair and some heat intolerance. If this be the source of the involved gene (or genes), the inheritance appears to fit well into the more widely accepted theory of transmission of a recessive factor by the female to a male offspring. It is unfortunate that the status of the great-grandmother's sudoriferous mechanism was not definitely known. Her being clinically anhidrotic is not inconsistent with known facts because eight out of sixty cases reviewed by Kaalund-Jorgensen and Christensen were women.[11] Weech[2] accounts for this apparent inconsistency in the theory of transmission by postulating that the dysplasia begins in a genic mutation, which may occur in patients of either sex. Thereafter, the described pattern of transmission by the female and expression in the male is followed.

Levitt[12] accounts for the occasional presence of the disease in females by the fact that in man most pathological mutations are not completely dominant or recessive. Thus, the genes of ectodermal dysplasia are considered "conditionally dominant" with sex linkage and would be evident in some women.

If the white great-grandmother be the source of the genic mutation, it is interesting to note that it was carried by two generations of Negro women before becoming evident in the third Negro generation.

That complete anhidrosis may not be present in all cases has been proposed by Felsher[13] whose patient appeared to have not only functioning apocrine glands but also 5 and 7 per cent of the normal number of eccrine glands in the forearm and thigh, respectively, by the Minors iodine-starch test. Because of these findings, they suggested hypohidrotic as a more accurate term. This was not found in our patient. It is more than likely though that there are varying degrees of deficiency in patients presenting clinical evidence of heat intolerance and probably both terms are applicable.

It has been shown by Loewy and Weehselman[1] that these patients apparently have normal insensible perspiration, indicating that the sweat gland apparatus is called into action only under conditions of increased demand and that normal insensible perspiration is probably conducted through other channels. Tendlau[1] has been able to demonstrate normal absorption function of the skin with potassium iodide which, when rubbed into the patient's skin, was present in the urine within six hours.

Although our patient's age was only 26 months, the dental department provided dentures which he can wear without apparent difficulty. He also inserts and removes them unaided when necessary.

In 1938, Kerley advised deferring dentures until the age of 10 years because "The dental processes had not developed sufficiently to hold them in position" and "on account of the disagreeable features connected with becoming accustomed to the artificial dentures."[14] While temperament and many other factors will modify each case, in our patient these objections were not apparent.

Brodie and Sarnat[15] indicated that complete anodontia does not impair development of the face and jaws. They based their opinion on serial x-rays taken from 1 year 10 months to 5 years 4 months of age which showed a normal pattern of growth.

We noticed after six months' observation that with the dentures in place

there is still some abnormal protrusion of the lower lip. This appears to contradict the supposition so often expressed that the lip protrusion is due to absence of teeth. Future long-term changes may, however, be more illuminating and reveal a more definite change.

In our experience, the dental problem per se certainly does not seem to be an unsurmountable one. We believe that for psychological and nutritional reasons dentures should be made at an early age and that they should be altered as growth and development proceed.

While it appears that our patient is the second American Negro, also of mixed ancestry, to be reported with this condition in the American literature, we believe this syndrome is not rare. We are convinced that, with time, it will be found in all races. This view is supported by Widderburn[7] and Thadani[9] each of whom described many cases in Hindu families around Sind, India; and de Silva[7] who described four cases from Ceylon—three in Singhalese and one in a Tamil.*

In addition, as pointed out by Clouston,[6] whereas previously many of these patients probably died of infections in early infancy, with the advent of antibiotics and chemotherapeutic agents, many will now survive to ages where the diagnosis can be more easily made.

SUMMARY

1. A case of anhidrotic hereditary ectodermal dysplasia is reported in a Negro boy of mixed ancestry. It seems that the boy inherited the disease from a white maternal great-grandmother.

2. It is suggested that this entity is more common than the literature indicates.

3. Dentures should be made for these patients at an early age.

*The peoples of India and Ceylon have not yet been well classified anthropologically. While the Sinds are generally considered Caucasians (Indoaryan), the Singhalese and Tamils have been classified at one time or other as Caucasians, Mongoloids, Africans, and Australoids.[16]

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CONGENITAL ENTERO-UMBILICAL FISTULA DUE TO A PATENT VITELLINE DUCT

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VARIOUS forms of intestinal pathologic lesions in infants and children have resulted from an arrest in the development of the vitelline duct. Conservative estimates of its frequency range from 1 to 3 per cent.[1, 2] When the omphalomesenteric or vitelline duct undergoes an incomplete involution leaving a continuous communication between the intestine and umbilicus, feces may be discharged at the umbilical orifice. Before presenting a case of congenital entero-umbilical fistula due to a patent vitelline duct a short summary of the historical background and regional development will be given.

HISTORICAL

In the early 1800's, Johann Frederic Meckel, the Berlin anatomist, discussed the anatomy and embryology of the vitelline duct and suggested its role in abdominal disease. Under anomalies of the intestinal canal he mentions,[3] "the more or less perfect continuance of its primitive connection with the umbilical vesicle." In referring to the major vitelline duct malformations, Meckel further states, "These three anomalies are only different degrees of the same deviation of formation. This is proved by their appearing always in the same place, by their connections with the omphalomesenteric vessels, and finally, the insensible shades which each presents in respect to length and size."

There has been a tendency to confuse the subject by considering all the anomalies of the vitelline duct as pathologic variants of a Meckel's diverticulum. Chamberlain[4] in 1949 stresses this attitude as being incorrect historically and illogical clinically and anatomically. It should be recognized that the vitelline duct is the fundamental structure, that the diverticulum of the ileum which bears Meckel's name is the commonest of several lesions resulting from an arrest in the development of the duct. The conditions characterized by a band, polyp, cyst, sinus, and fistula are rare entities of the omphalomesenteric duct itself, and as such are on a similar plane with Meckel's diverticulum.

REGIONAL EMBRYOLOGY[5]

On the under surface of the inner cell mass, cells appear and arrange themselves in a definite sheet, the entoderm. This entoderm by subdivision and formation of a central cavity fashions itself into a small yolk sac. The splanchnic mesoderm overlying the nutritionally vestigial yolk sac bears the vitelline vessels. In the 3-week-old human embryo the roof of this yolk sac by a process of evagination begins to fashion the fore and hind guts which are then connected by a slightly narrower region to the yolk sac proper. The isthmus of yolk sac tissue connect-

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ing gut with yolk sac proper normally grows at a much slower rate, becoming drawn out and forming a duct, the omphalomesenteric duct, which soon is incorporated into the umbilical cord.

Between the fourth and the tenth week of fetal life the intestine takes up a temporary location in the umbilical cord. By the end of the tenth week as the intestine is retracting into the abdominal cavity, the umbilicus starts to close. During this time the vitelline duct is usually undergoing obliteration.

Normally, by the fifth month of fetal life the fibrous strand of vitelline duct lying between the umbilicus and bowel has become detached, atrophied, and absorbed. Should there be a failure of the orderly degenerative process any one of the numerous congenital anomalies of the omphalomesenteric duct may result.

CASE REPORT

B. S., a white male infant, weighing 3,860 grams, was delivered at term under caudal anesthesia on April 8, 1951. No apparent abnormalities were observed at this time. Routine care consisting of clearance of the air passages, use of 1 per cent silver nitrate solution in the eyes, and clamping of the umbilical cord with the Funis clamp was instituted.

The entire pregnancy and labor were uneventful. There was one other healthy female sibling and no history of any abortions or miscarriages. Both presents were in good health. The family history for congenital or hereditary disorders was negative.

The Funis clamp was removed one day after birth. On the morning of April 11, the nurse reported that the umbilical cord was apparently infected and draining. The infant had been retaining an evaporated milk formula, had been passing normal meconium stools, appeared well hydrated, and was afebrile. Examination of the infant revealed an area of redness surrounding the umbilicus. Slight pressure applied over this region resulted in the extrusion of meconium from the umbilicus (Fig. 1). There were no untoward signs or symptoms suggesting that a loop of gut might have originally been caught in the Funis clamp. The clinical impression was that of an entero-umbilical fecal fistula due to persistent vitelline duct.

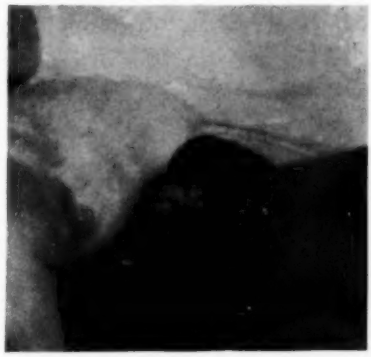

Fig. 1.—Meconium stool protruding from the proximal segment of umbilical cord.

The baby was transferred from the nursery to the pediatric ward. On admission, hemoglobin was 18 Gm. per 100 c.c., red blood count 4.9 million per cubic millimeter, white blood count 8.0 thousand per cubic millimeter with a differential of 50 per cent polymorphonuclear leukocytes, 44 per cent lymphocytes, and 6 per cent monocytes. The urinalysis was negative.

On the sixth day of life operation was performed. Preoperative management included parenteral fluids intravenously, prophylactic vitamin K, penicillin, and streptomycin. Under open drop ether vertical and circumumbilical incisions were made. The omphalus, including excessive peritoneum and vitelline duct, was excised to less than 1 cm. from the terminal ileum. The stump of the intestinal portion of the duct was turned in two layers. Some excess skin was left to

permit formation of an umbilicus. The specimen (Fig. 2) consisted of an umbilicus attached to a length of vitelline duct which opened on to the surface of the umbilicus and had a cherry-red color. The microscopic picture of a section (Fig. 3) of the vitelline duct contained aberrant pyloric, and intestinal mucosa.

The postoperative course was uncomplicated, a dilute evaporated milk formula being introduced twenty-four hours after surgery. The infant was discharged on the twelfth day of life

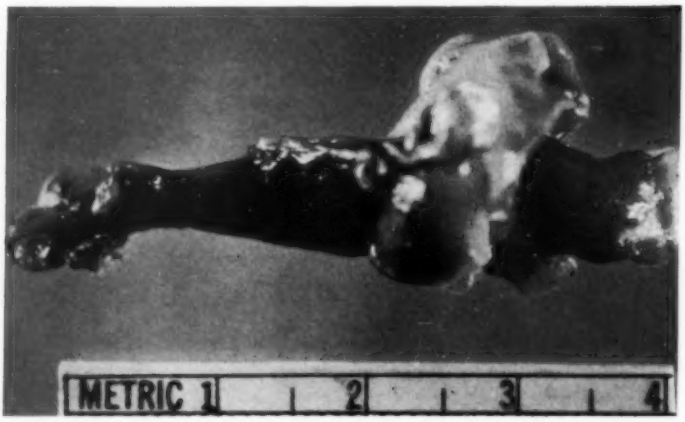

Fig. 2.—Gross specimen of patent vitelline duct from our case.

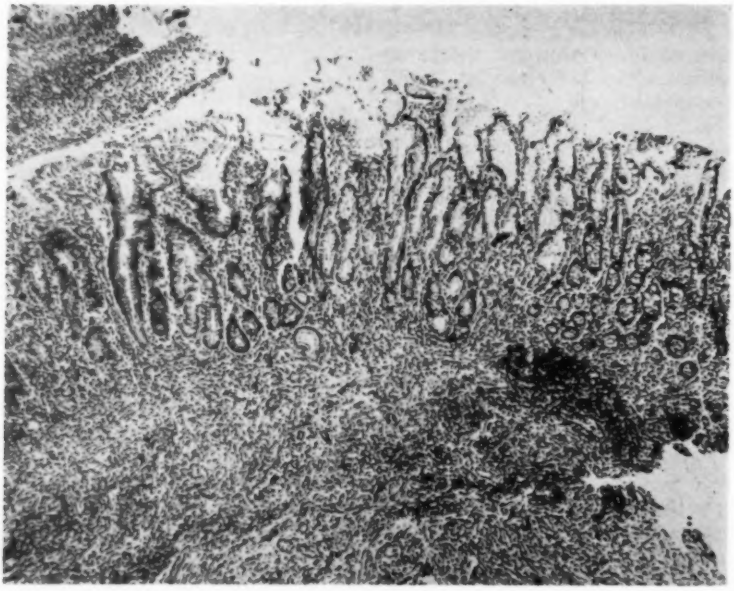

Fig. 3.—Photomicrograph demonstrating heterotopia. Pyloric mucosa on the left and intestinal mucosa on the right.

weighing 3,674 grams, and passing normal stools per rectum. Complete healing of the umbilical incision had occurred. Follow-up at the age of 8 months revealed an apparently normal, healthy baby.

DISCUSSION

There have been no previous reviews of this condition in the American pediatric literature, although it is not unknown in textbooks and surgical journals. Cullen,[6] in his classical book, *The Umbilicus and Its Diseases,* published in 1916, described more than forty cases of patent vitelline duct that had been reported until then.

Kittle and associates[7] in 1947 reviewed the literature on patent vitelline duct and added two cases of their own which had occurred in over 30,000 deliveries during a ten-year period at the Chicago Lying-In Hospital. This brought the total number of cases reported till then to 131, and included several which had been discovered at autopsy on premature infants.

An exhaustive search of the literature by ourselves revealed reports of the following twelve additional cases bringing the total to 143 cases of patent vitelline duct, not counting our own case. Ferguson[8] in June, 1948, reported sixty-eight cases of umbilical anomalies occurring at the University Hospital, Ann Arbor, Mich., between 1925 and 1947. Eight of these were cases of patent vitelline duct. In April, 1946, Howell[9] listed sixty-one cases of Meckel's diverticulum found in 122,490 admissions during a ten-year period (1934 to 1944) at Duke Hospital. Of these, only one was mentioned as being in the form of a patent omphalomesenteric duct. A study of all the available material at the Mayo Clinic through 1943 dealing with congenital lesions in or near the vicinity of the umbilicus was reported by Trimingham and McDonald[10] in 1945. Of their twenty-four cases, only one was that of a completely patent omphalomosenteric duct. Ladd and Gross,[11] in their book *Abdominal Surgery of Infancy and Childhood* published in 1941, recorded only one case of a completely patent vitelline duct in discussing operative results in seventy-three cases of Meckel's diverticulum. Their one case resulted in a surgical mortality. In July, 1950, Arnheim[12] reported the fourth surgical cure of a case of patent vitelline duct complicated by small bowel prolapse.

The 144 cases of patent vitelline duct (including our own) may be divided into two groups of 113 and 31 cases, respectively, depending upon whether or not they were uncomplicated. The second group of thirty-one cases represents cases in which the patent ducts were complicated by a prolapse of small intestine though the umbilical fistula. Kittle grouped his cases similarly. However, we feel that three of the cases originally placed by Kittle in Group 1 actually belong in Group 2. Two of the cases were reported by Mathews[13] in 1925 and by Montgomery[14] in 1938 in which at birth irreducible congenital umbilical hernias as primary pathology were noted, necessitating s u r g i c a l intervention within twenty-four hours. Associated with the hernia and possibly predisposing to them, patent vitelline ducts were found. The third case reported in 1843, and described by Cullen[6] in his book, was that of an infant with a patent duct and a complicating prolapse that underwent a spontaneous reduction. However, the infant succumbed shortly afterward from thoracic disease, probably tuberculosis.

Tables I*A* and I*B* indicate that entero-umbilical fistula due to patent vitelline duct is more prevalent among males, and is usually discovered during the neonatal period. There has been only one report of persistent vitelline duct occurring in twins. Garrett[15] in 1928 reported the case of female homozygous twins who showed an umbilical discharge from such a patency during their second week of life. Tables II and III list the types of therapy and the results. The complicated cases with the concomitant bowel prolapse make up 20 per cent of the total number of cases. From the same tables it can be seen that prolapse augurs a grave prognosis, surgical resection offering the only small chance for recovery.

We consider our case noteworthy because of two unusual features, namely, early diagnosis and early surgical therapy. By using the Funis clamp with its early removal after twenty-four hours a diagnosis was made possible before the navel cord had fallen off. This is in contrast to those textbooks of surgery[16] where it is stated that the diagnosis may become apparent only after the umbilical cord falls off and one sees a bright red nodule, varying from pea to walnut size, probably representing the mucosa of the everted end of the patent duct. In our case, abdominal pressure re-

TABLE IA. SEX DISTRIBUTION OF REPORTED CASES

M	F	UNKNOWN
99	17	28
69%	12%	19%

TABLE IB. AGE AT WHICH PATENT UMBILICAL FISTULA WAS DISCOVERED*

TOTAL	BIRTH TO 2 WK.	2 WK. TO 1 MO.	1-2 MO.	2-6 MO.	6 MO. TO 1 YR.	1-3 YR.	3-5 YR.	OVER 5 YR.	AGE UNKNOWN OR AUTOPSY REPORT
144	49	12	8	20	12	10	5	9	19

*It is probable that some of the cases in the older age groups may actually have occurred at an earlier period.

TABLE II. TYPE OF THERAPY INSTITUTED IN REPORTED CASES OF PATENT VITELLINE DUCTS

TYPE OF CASE	TREATED		UNTREATED	NO MENTION AS TO THERAPY	TOTAL
	CONSERVATIVE*	RESECTION			
Complicated	8	13	9	1	31
Uncomplicated	22	67	12	12	113

*Conservative therapy included ligation, caustics, curettage of tract, or occlusion apparatus.

TABLE III. RESULTS IN TREATED AND UNTREATED COMPLICATED AND UNCOMPLICATED CASES OF PATENT ENTERO-UMBILICAL FISTULA

		NO. OF CASES	SURVIVED	DIED
Complicated Cases		8	0	8
Treated	Conservative	13	4	9
Untreated	Resection	9	0	9
Uncomplicated Cases		22	19	3
Treated	Conservative	67	59	8
Untreated	Resection	12	3	9

sulted in extrusion of feces through the stump of the umbilical cord, whereas with the usual cord tie this would not have resulted until the cord had fallen off completely. The second factor of significance is a natural outcome of early diagnosis. So far as can be ascertained our case represents the earliest report of surgical intervention in the uncomplicated form reported in the English speaking literature. This is important when we consider that prompt surgical therapy aborts the possibility of prolapse and decreases the possibility of secondary skin infection. Of the thirty-one cases of prolapse, twenty-one occurred in the first month of life.

SUMMARY

1. A case of congenital entero-umbilical fecal fistula due to a patent vitelline duct has been reported.

2. An unusual feature resulting in early diagnosis and consequently earlier therapy was directly related to the use of a Funis clamp instead of a cord tie.

3. A review of the literature has been made with special emphasis on sex, age of occurrence, and therapy of congenital entero-umbilical fistula due to patent vitelline duct.

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EXPERIMENTAL GLUTAMIC ACID TREATMENT IN MENTALLY RETARDED CHILDREN

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PRICE, Waelsch, and Putnam[9] demonstrated in 1943 that glutamic acid had a salutary effect on children with petit mal, in so far as the seizures decreased in frequency and the general activity of the patients increased.

The results of maze tests conducted by Zimmerman and Ross[14] on white rats suggested that the addition of glutamic acid to the food enhanced their teachableness.

Albert and Warden[1] conducted similar tests on white rats in a problem box and were able to show that increased glutamic acid in the animals' food served to raise their level of intelligence.

Neither Stellar and McElroy[11] nor Marx[11] and Hamilton[11] were able to verify these observations.

Albert, Hoch, and Waelsch[2] experimented with glutamic acid in nine children with secondary mental retardation, postencephalitic and otherwise, each patient being given glutamic acid and a substitute alternately. In seven of these cases the I.Q. rose by about 5 to 10 units after a few months' treatment.

In several papers published between 1946 and 1950, Zimmerman, Burgemeister, and Putnam,[15-19] of the Neurological Institute, Columbia University, New York, have since demonstrated the effect of glutamic acid on feeble-minded children with and without epilepsy. The maximum effect, they found, occurred after at least six months' treatment and the doses had to be adapted to the patients' reactions (motor irritation with increased reflexes and general unrest), being about 20 to 30 Gm. per day for children in general (increasing doses in later papers). Particularly interesting results were obtained with glutamic acid treatment in a series of thirty-five slightly mentally retarded children with intelligence quotients of from 55 to 79, which in one-third of them rose to between 80 and 89 after one year's treatment. The results were poorer in children with organic brain lesions, behavior disorders, or emotional instability. In most cases the children were outpatients.

Several papers in recent years have reported contradictory results; Kandik,[4] for instance, having summed up his results as being not convincing. Quinn and Durling[10] report a slight rise of the I.Q. in a series of outpatients without controls. In a clinical series with controls, comprising forty-three cases, McCulloch[7] has found no effect of glutamic acid. Kerr and Szurek[5] describes a very small series which scarcely permits definite evaluation. Loeb and Tuddenham[6] have a very carefully arranged inpatient series grouped in pairs with controls and comprising thirty-three cases, in which they have found no difference following glutamic acid treatment. This series has been treated statistically with analysis of variation.

From the Linköping Children's Hospital.

In a series of institutionalized feeble-minded children carefully observed in 1949 and 1950 under the alternate administration of glutamic acid and a substitute preparation, Hellström and Melin found no salutary effect of glutamic acid (personal communication to the writer). These patients were also studied by means of electroencephalograms.

According to Weil-Malherbe,[13] the action of glutamic acid is due to the fact that it is the only amino acid oxidized direct by the cerebral substance; and according to Nachmansohn and Machado[8] the action occurs via a resynthesization of cholinacetylase.

Early in 1951, Astrup and Munkvad[3] described the chemistry and physiology of glutamine and glutamic acid.

PERSONAL INVESTIGATIONS

In the spring of 1950 certain experiments were conducted at Storängen Children's Home, Söderköping, the County of Östergötland Institution for Mental Defectives, in collaboration with the principal and teaching staff at the home, to elucidate the possibilities of improving the intelligence quotient in a series of feeble-minded children by administration of l (+) glutamic acid. The cost of the latter was borne by the Östergötland County Council. In these experiments we used l (+) glutamic acid, the chemical and physical properties of which had been tested by the responsible control laboratory. The manufacturing chemists, AB Astra, were kind enough to make up the glutamic acid in a suitable granular form and to produce a substitute preparation having a somewhat similar taste and smell.

The group was taken, without regard to sex, from the school groups comprising "educable feeble-minded" children between the ages of 7 and 15 years, with an I.Q. ranging from 42 to 77. To preclude or reduce the possibility of variations in the I.Q. due to environment, tuition, etc., only such children were taken as had been under observation at the school for at least two terms. Where possible we sought by studying the history to exclude children with organic lesions. Full neurological examinations were carried out in each case, but no electroencephalograms were taken. All urine samples were negative for phenylpyruvic acid. Although no detailed psychologic investigations were undertaken, we endeavored to select only children considered reasonably well balanced and tractable, so that the medication could be carried out satisfactorily. Testing was done according to forms L and M of Terman and Merrill's modification of the Stanford-Binet scale, arranged and translated by Alice Hellström.[12] All the tests were carried out by the children's own teachers, who had already tested them earlier. Since the experiments had been planned for 1949 the children were tested in the spring and fall of that year, so that in many cases a year had elapsed since the tests when the glutamic acid treatment was instituted in January, 1950. Nor was it always possible, as will be seen from the tables, to conduct the final tests immediately after the conclusion of treatment.

Glutamic acid was administered to sixteen children in doses of 6 Gm. three times a day from Jan. 14 to May 20, 1950, without any demonstrable side effects (see, however, the case report on patient S. H.). The teachers and school nurse saw to it that this

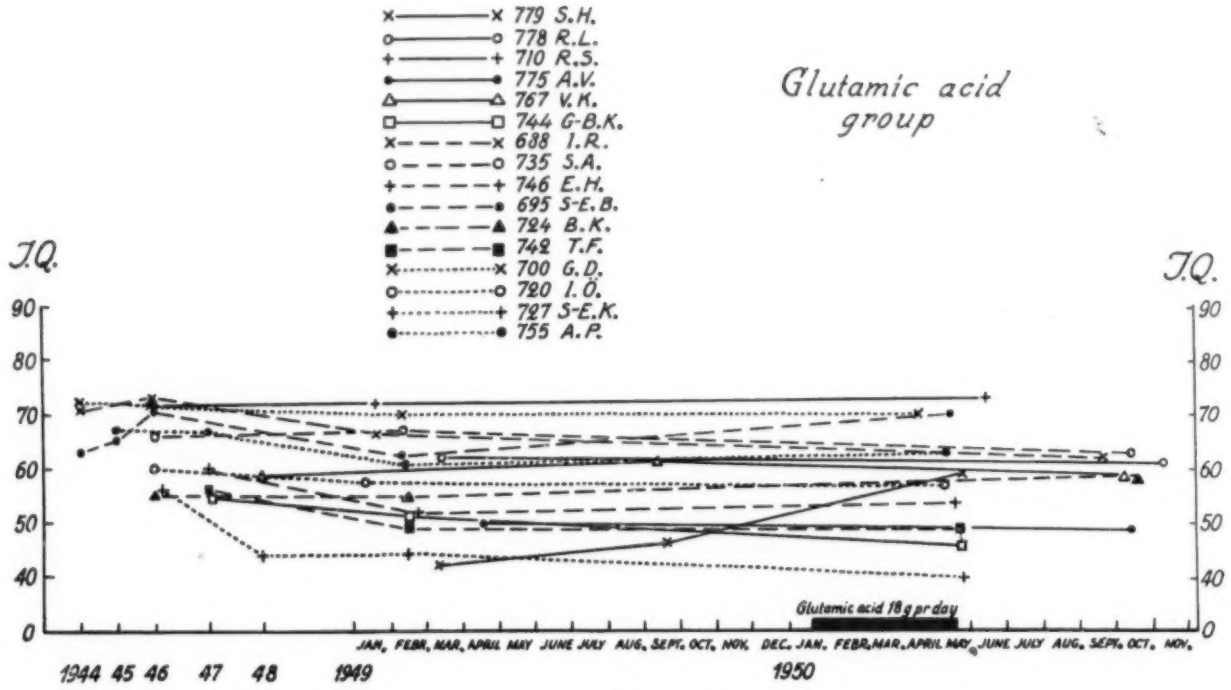
779 S.H.
778 R.L.
710 R.S.
775 A.V.
767 V.K.
744 G-B.K.
688 I.R.
735 S.A.
746 E.H.
695 S-E.B.
724 B.K.
742 T.F.
700 G.D.
720 I.O.
727 S-E.K.
755 A.P.
Glutamic acid group
I.Q.
I.Q.
90
80
70
60
50
40
0
Glutamic acid 18 g pr day
JAN. FEBR. MAR. APRIL MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEBR. MAR. APRIL MAY JUNE JULY AUG. SEPT. OCT. NOV.
1944 45 46 47 48 1949 1950

Fig. 1.

scheme was adhered to. A granulated substitute was administered to a control group of fifteen children whose ages and intelligence quotients coincided as closely as possible with the others. It had been hoped to preclude identification of the two groups, but unfortunately the substitute did not have such a disagreeable taste as the glutamic acid, so that they could be differentiated immediately.

The glutamic acid treatment, as is evident from the curves and tables, was not very successful. In the glutamic acid group (Table I and Fig. 1), the quotients were more or less the same before and after treatment, with minor variations in both directions within the errors of method and within the range of the earlier values. Only in one case did a conspicuous improvement occur, but it could not be attributed to the glutamic acid, being due rather to environmental factors.

This patient, S. H., was admitted to the Storängen institution in the spring of 1949 at the age of 7 years. Her I.Q. was 42 on admission and had risen to 47 by the fall. Since we then thought the rise had ended, it was decided to include her in the present series—the group she came into was, of course, purely fortuitious. She was easily irritated from the start, and under glutamic acid treatment became even more irritable, but she presented none of the gastrointestinal disturbances and insomnia symptoms that are reported to attend such treatment. Following the glutamic acid treatment her I.Q. had risen in May, 1950, to 59. This rise, however, did not finish with the discontinuance of treatment; on the contrary, it proceeded at such a rate that by February, 1951, her I.Q. was as high as 70. The child's teachers were convinced that she had derived great benefit from the change of environment, that her previous environment had been comparatively unfavorable, and that no significance could be attributed to the glutamic

TABLE I. GLUTAMIC ACID GROUP
I.Q. According to Terman and Merrill Forms L and M

INITIALS	NO.	YEAR OF BIRTH	I.Q.								
			1944	1945	1946	1947	1948	1949		1950	
								MONTH	I.Q.	MONTH	I.Q.
S. H.	779	1942						Mar.	42	May	59 M
								Sept.	47 M		
R. L.	778	1940						Mar.	62	Nov.	61 L
R. S.	710	1939						Jan.	71 M	June	73 M
					72						
					71						
A. V.	775	1939						Apr. ?	50	Oct.	49 L
V. K.	767	1938					59	Sept.	62 M	Oct.	59 M
G-B. K.	744	1938						Feb.	52 L	May	46 L
						54					
I. R.	688	1937	71		73			Jan.	66 L	Sept.	62 L
S. A.	735	1937			66			Feb.	67 L	Oct.	63 L
E. H.	746	1937				60		Feb.	52 L	May	54 L
S-E. B.	695	1936	63	65	71			Feb.	63 M	May	70 M
B. K.	724	1936			55			Feb.	55 L	Oct.	58 L
T. F.	742	1936				56		Feb.	49 L	May	49 L
G. D.	700	1935	72		72			Feb.	70 L	Apr.	70 M
I. Ö.	720	1935			60			Jan.	57 L	May	57 L
S-E. K.	727	1935			56		44	Feb.	44 L	May	40 L
A. P.	755	1936		67		67		Feb.	61 L	May	63 L

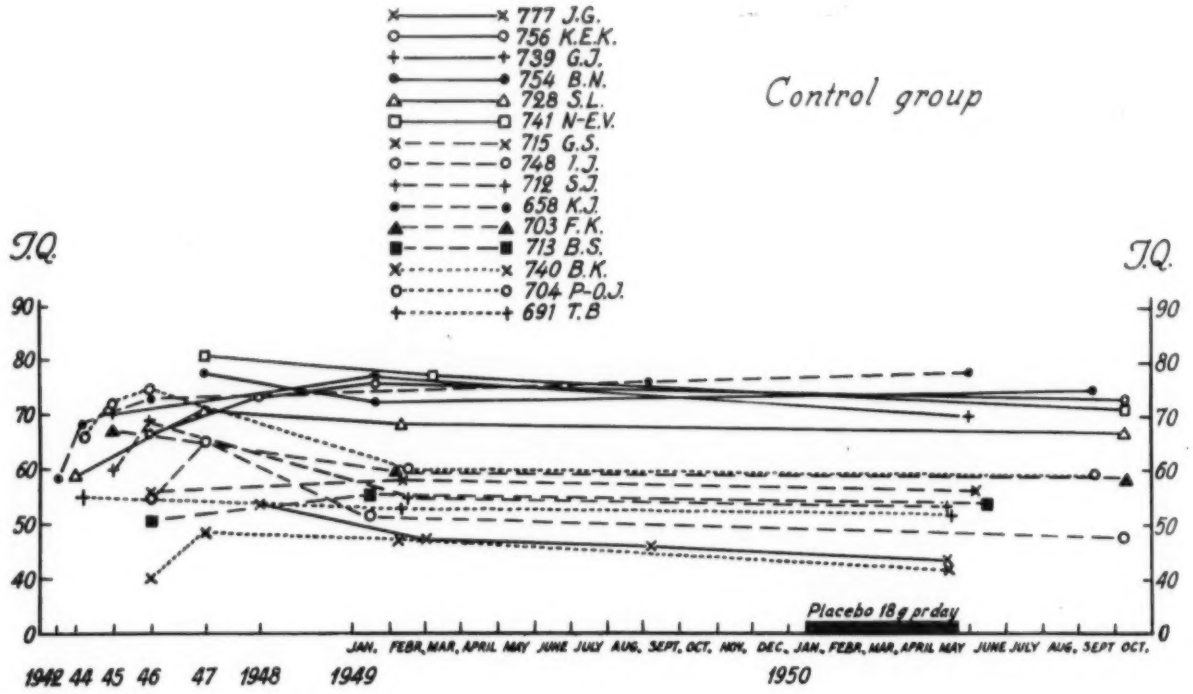
777 J.G.
756 K.E.K.
739 G.J.
754 B.N.
728 S.L.
741 N-E.V.
715 G.S.
748 I.J.
712 S.J.
658 K.J.
703 F.K.
713 B.S.
740 B.K.
704 P-O.J.
691 T.B
Control group
I.Q.
I.Q.
90
80
70
60
50
40
0
Placebo 18 g pr day
JAN. FEBR. MAR. APRIL MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEBR. MAR. APRIL MAY JUNE JULY AUG. SEPT OCT.
1942 44 45 46 47 1948 1949 1950

Fig 2.

acid. Cases have been reported from America in which the I.Q. has continued to rise following the termination of glutamic acid treatment; but if the latter is to be ascribed any role we must first be able unreservedly to exclude environmental factors as a major cause. In the present case we have a continuous rise as from the time of admission, which fact strongly suggests an environmental influence.

As regards the question of deleterious effects it should be pointed out that, aside from the increased irritability in patient S. H., the glutamic acid had no demonstrable side effects. Whether this was due to the low dosage has not been possible to establish. The neurological findings were the same before and after treatment.

In the control group (Table II and Fig. 2) treated with a substitute containing sucrose and lactose, while the other group received glutamic acid, the I.Q. showed on the whole the same values before and after the experiment.

DISCUSSION

It might be objected to that the present experimental investigation was of too short duration. According to Zimmerman, Burgemeister, and Putnam the duration should be at least six months, and preferably one to two years. The dosage, too, was low, 18 Gm. per day. It is desirable, as previously mentioned that the dose be adapted to each individual case, and preferably raised to the threshold of motor irritation, with increased reflexes and general unrest, which was not done in this series. The maximum dosage in children has been given as about 30 Gm. per day. The dose used here might, however, be considered fairly high; some investigations have been published, especially in 1946 and 1947,[4, 5] in which the dose was invariably from 8 to 10 or from 6 to 24 Gm. per day. Moreover, the duration of treatment was just over four months; and there are published results where the effect on the I.Q. has been attributed to glutamic acid after treatment lasting only

TABLE II. CONTROL GROUP
I.Q. According to Terman and Merrill Forms L and M

INITIALS	NO.	YEAR OF BIRTH	I.Q. 1942	1944	1945	1946	1947	1948	1949 MONTH	1949 I.Q.	1950 MONTH	1950 I.Q.
J. G.	777	1942						53	Mar. Sept.	47 46 M	May	43 M
K-E. K.	756	1941				67		74	Jan.	76 M	Oct.	73 M
G. J.	739	1940			70				Jan.	77 L	June	70 L
B. N.	754	1939					77		Jan.	73 L	Sept.	75 L
S. L.	728	1939		59			71		Feb.	68 M	Oct.	67 M
N-E. V.	741	1938					81		Mar.	77 M	Oct.	72 M
G. S.	715	1938				56			Feb.	58 M	June	57 M
I. J.	748	1938				55	65		Jan.	51 M	Oct.	48 M
S. J.	712	1937			60	69			Feb.	56 L	May	54 L
K. J.	658	1936	58	68		73			Sept.	77 M	June	78 M
F. K.	703	1936			67				Feb.	60 L	Oct.	58 L
B. S.	713	1936				51			Jan.	55 L	June	54 L
B. K.	740	1936				40	48		Feb.	47 L	May	42 L
P-O. J.	704	1935		67	71	74			Feb.	60 M	Sept.	59 M
T. B.	691	1935		55					Feb.	53 L	May	53 L

two or three months, and where it has subsided when the administration was discontinued, thus suggesting that the change was due to glutamic acid. Hence, it should have been possible to obtain in four months an effect equal to that reported by Albert, Hoch, and Waelsch.[2] However, the American investigations have been conducted almost exclusively with outpatients, with all that this implies in the way of uncontrollable environmental influence; and, moreover, the control series in many cases have been meager and of unsuitable composition. For instance, in the mongolism series[17] there was no control group comprising mongols, although this might well have seemed feasible bearing in mind that as many as thirty mongol children and young persons were available. Instead, the control series consisted of mentally retarded children without mongolian characteristics.

I venture to claim that although the dosage was on the low side and the duration somewhat short, the present investigation is of some value because it was conducted on a series of mentally retarded children with fairly uniform levels of intelligence (I.Q. 42 to 77) and assignable to a not unduly large age group (7 to 15 years), being therefore fairly homogeneous; and because the environmental factors were quite unchanged throughout the investigation and were identical in the two groups. Hence, any effect that might have been present should have been demonstrable. A study of the respective figures shows, it is true, that the I.Q. was constant in the glutamic acid series (patient S.H. included, a rise of 0.31 unit; excluded, a fall of 0.47 unit), but fell by 2 units in the control series; yet the difference is too small to be ascribed any significance, at all events in this limited material.

As regards the number who "improved," i.e., who showed a rise in the I.Q., we find six of sixteen or five of fifteen (including or excluding patient S. H.), with a mean rise of only 3.2 units, in the glutamic acid group, and in two of fifteen, with a mean rise of 1.5 units, in the control group. Even though a somewhat greater tendency to improvement was thus evident in the glutamic acid group, it was probably too slight to have any value in such a small series.

The results of this investigation would seem to warrant the supposition that l (+) glutamic acid does not gence quotients of mentally retarded have the salutary effect on the intellichildren that previous investigations had led one to expect.

SUMMARY

Granulated l (+) glutamic acid was administered to a series of sixteen children between the ages of 7 and 15 years, with intelligence quotients ranging from 42 to 77, at Storängen Children's Home, Söderköping, for the purpose of studying its effect on the intelligence quotient. The dosage was 18 Gm. per day in three doses, and the duration of treatment just over four months.

A control group comprising fifteen children of corresponding ages and intelligence was treated concurrently with a granulated substitute.

The treatment had no demonstrable effect.

The Östergötland County Council made a grant for the purchase of glutamic acid. The latter was tested by Apotekens Kontrollaboratorium. AB Astra kindly prepared the granulated glutamic acid and the substitute.

The investigation was conducted at the County of Östergötland Institution for Mental Defectives, Storängen Children's Home, Söderköping, with the coöperation of its Principal, Miss Margareta Udén, the teachers, Miss Karin Fornander, Mrs. Inga Olsson, Miss Ingrid Bergman, Mrs. Anna-Greta Blom, and Mr. Eric Geijer, and the school nurse, Sister Ella Franzenius.

The writer wishes to record her grateful acknowledgments to the above institutions and persons.

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BACTERIOSTATIC, GERMICIDAL, AND SANITIZING ACTION OF QUATERNARY AMMONIUM COMPOUNDS ON TEXTILES

II. Sanitization of Cotton Fabrics

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In a previous study,[1] the bacteriostatic values of five selected quaternary ammonium salts against the test organism *Proteus mirabilis* were clearly defined. It seemed important, therefore, to extend the studies on these compounds to determine their relative efficiency as sanitizing agents for cotton fabric and to clarify the existing information on their practical value for this use.

Recent investigations on the efficiency of quaternary ammonium compounds as sanitizers and disinfectants for laundry have employed bacterial plate counts on rinse waters to provide an index to the sanitizing and germicidal value of these products. Evidence of the sanitizing value of alkyl dimethyl benzyl ammonium chloride, used in a dilution of 1:5,000 at 40° C., was advanced by Lawrence and Murphy and reported by Lawrence.[2] The results of their plate count studies on the first and second deep rinses in machines of Westinghouse Laundermat type tend to support the contention of Bartlett,[3] that quaternary ammonium compounds can be used to assure sanitary finished laundry. They are, however, directly contrary to the conclusion drawn by Mack[4] that the use of bacteriostatic quaternary ammonium salts does not reduce the total bacterial counts or counts of *Escherichia coli* in laundry.

A review of the literature reveals that very little scientific information is available concerning mechanical removal of microorganisms from fabrics as opposed to the bactericidal effects of soaps, bleaches, heat, etc., during laundering. Roberts,[5] using a standardized inoculum on fabric, recovered a total of 38 per cent of the original inoculum from a series of five rinse waters as determined by plate counts of viable organisms. She reported that in procedures using one suds and two rinses, only 20 to 50 per cent of the original inoculum was eliminated from the fabric. For this reason, it is believed that sterile laundry rinse waters cannot be employed as an absolute index to sterile laundered fabrics nor final evidence of the elimination from the fabric itself of a specific infectious agent.

However, if sanitization can be defined as a treatment which reduces the bacterial count to a relatively safe level, it might be conceded that a reduction of the bacterial count in laundry rinse waters of 99.9 per cent or more could be accepted as a practical presumptive index to sanitizing efficiency. In actual practice a reduction of this magnitude in the rinse might even be employed as a presump-

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tive index for disinfection since the surviving 0.1 per cent might consist entirely of resistant sporeforming cells of nonpathogenic species against which the usual chemical germicides are known to be ineffective.

In experimental rinse waters where resistant sporeforming bacteria have been eliminated from consideration, and the only bacteria present are cells of a selected nonsporeforming test organism, a reduction of 100 per cent in the rinse would be the minimum reduction that could be accepted as a presumptive evidence of disinfection. However, in test procedures of a similar type a lesser reduction of 99.9999 per cent has been accepted as an index to potential value with chemical sanitizers for dishes and eating utensils by the U. S. Public Health Service.[6] Acceptance of 99.9 per cent reduction of the inoculum as determined by plate counts of viable cells in a rinse as a significant end point for sanitizing action in these studies seemed practical. For it would be reasonable to assume that a reduction of this magnitude might have practical significance in the day-to-day maintenance of sanitary conditions in home and commercial laundries where specific infectious agents were not known to be present. It should be pointed out also that the selection of an end point at a higher percentage level would have required the use of a greater number of determinations in these studies than seemed feasible, if results were to be statistically reliable.

PROCEDURE

As in previous investigations the following five quaternary ammonium compounds were employed: (A) para diisobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride; (B) alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride; (C) alkyl (C_6-C_{12}) naphthyl methyl pyridinium chloride; (D) dodecyl acetamido dimethyl benzyl ammonium chloride; and (E) cetyl trimethyl ammonium bromide. Henceforth these compounds will be referred to as quaternary A, quaternary B, etc. The dilutions tested ranged from 1:5,000 to 1:100,000, or from 1 oz. quaternary for 9.4 lb. of dry fabric to 1 oz. quaternary for 187 lb. of dry fabric.

Cotton, gauze-type diaper cloth was used as the carrier for the test organism. Two dry samples of this cloth, 4 by 5 inches, weighed 3 grams. Two test strips folded to fit conveniently into each Petri dish were autoclaved for twenty minutes at 250° F., then dried in a hot air oven at 105° C.

The test organism was a typical strain of *E. coli* having an average resistance of 1:90 to phenol, as determined by the method of the Association of Official Agricultural Chemists.[7] The stock culture was maintained at 5° C. on Bacto-Tryptone Glucose Extract Agar slants (T.G.E.)— tryptone 5 Gm., glucose 1 Gm., beef extract 3 Gm., agar 15 Gm., distilled water 1,000 c.c., with monthly transfer during the course of these studies.

For the inoculum 1 c.c. of a twenty-four-hour T.G.E. broth culture of the organism was used to seed Kolle flasks containing 60 c.c. of T.G.E. agar. After incubation at 37° C. for twenty-four hours, the surface growth was removed with 50 c.c. of sterile distilled water and a homogeneous preparation obtained by filtration through coarse paper, Schleicher and Schull, No. 588. The heavy suspension of cells was diluted to give a 50-60 reading on

Klett-Summerson photoelectric colorimeter using No. 42 blue filter. This suspension, on further dilution of 1:20, provided a standard inoculum of approximately 10,000,000 cells per cubic centimeter.

Each two samples, or 3 grams of fabric, were inoculated with 4 c.c. of the standardized cell suspension and introduced into a pint jar containing 96 c.c. of medicant. Determinations were made in duplicate for each dilution of each quaternary. For controls, two samples of fabric similarly inoculated were placed in a jar containing sterile distilled water.

On the assumption that approximately 50 per cent of the organisms may remain on the cloth, the inoculum described above yielded a fabric-water preparation containing on the order of 300,000 bacteria per cubic centimeter of extractable liquid, which is roughly equivalent to numbers reported to be found in final rinse waters of home laundries.[8]

The jars were transferred to a launder-ometer where they were agitated at indicated temperatures for fifteen minutes. Each sample was twisted with sterile forceps to express the liquid, then introduced into a test tube containing 20 c.c. of 5 per cent distilled water solution of Tamol N.[9] After ninety minutes' exposure in the Tamol N to assure complete neutralization of excess quaternary, the samples were discarded and dilution plate counts on the rinse waters in the tubes were made using T.G.E. agar.

Counts were made in duplicate from two rinse tubes selected to yield data from the duplicate quaternary treatments at each dilution tested.

The counts on the distilled water controls were used as a base for determining the per cent of organisms surviving exposure to the various dilutions of quaternaries according to the following formula:

$$\frac{\text{Average number of colonies per c.c. rinse after exposure to quaternary}}{\text{Average number of colonies per c.c. rinse of control fabric.}} \times 100.$$

The per cent reduction of viable organisms was obtained by deducting from 100 the figures obtained as above.

When the experimentally contaminated fabric was exposed to dilutions of 1:5,000 quaternary, 1 c.c. and 0.1 c.c. aliquots of the neutralizer rinse provided countable plates. Dilutions of 1:10, 1:100, and 1:1,000 of Tamol N yielded, in most instances, plates with 30 to 300 colonies when the fabric was treated with dilutions ranging from 1:10,000 to 1:100,000 quaternary. From the control Tamol N tubes, dilution plates of 1:100, 1:1,000, and 1:10,000 were necessary to obtain similar data. Colonies were enumerated in a Quebec counter after forty-eight hours' incubation at 37° C.

RESULTS AND DISCUSSION

The results show that, in general, each quaternary at each temperature exhibits an increasing effectiveness with increasing concentration against the test organism *E. coli*, as determined by survival of viable cells in the Tamol neutralizer rinse. The five quaternaries were more efficient in reducing numbers of this organism at 45° C. than they were at 20° C. Sanitization, i.e., a 99.9 per cent reduction of the contaminating organisms, required for all five quaternaries 1:5,000 dilution, or 1 oz. quaternary to 9.4 lb. of cloth, when applied at 45° C. for fifteen minutes. At 20° C., quaternaries B and D showed a similar activity.

Quaternaries A, C, and E approached this effectiveness with more than 99 per cent destruction. Quaternaries B, C, and D, when applied at 45° C. in dilution of 1:10,000, or 1 oz. of quaternary to 18.7 lb. of cloth, also brought about more than 99 per cent reduction in numbers. It should be pointed out that the reductions above 99 per cent but less than the 99.9 per cent selected as an end point for this study cannot be considered as absolute evidence of failure to sanitize since differences of this magnitude probably fall within the range of experimental error in the counting methods used.

That reduction in count seems to depend on the concentration of quaternary and temperature of application is evident since there is, in general, a gradual diminution of cells from no reduction in certain instances to 99.9 per cent. The concentration and temperature relationship was noted also in studies relating to bacteriostatic effects of these compounds.[1] There it was shown that fabric treated with dilutions ranging from 1:25,000 to 1:100,000 for ten minutes at 45° C. subsequently inhibited the growth of *P. mirabilis* for sixteen hours, whereas fabric inoculated with *E. coli* prior to treatment with these same quaternaries for fifteen minutes at 45° C. required a dilution of 1:5,000 to bring about sanitization. In spite of the longer exposure period, five to twenty times the concentration of the quaternaries were required to sanitize the fabric than to render it bacteriostatic for sixteen hours. With high temperature applications it appears possible, therefore, to secure fabrics which have temporary residual bacteriostatic effects at lower concentrations than are required to secure a practical sanitizing benefit.

TABLE I. REDUCTION IN VIABLE CELLS OF *E. coli* WHEN THE INOCULATED FABRIC WAS EXPOSED FOR FIFTEEN MINUTES AT 20° C. AND AT 45° C.

Quaternary dilution		1:100,000	1:50,000	1:25,000	1:10,000	1:5,000
Ounce quaternary: pounds dry fabric*		1:187	1:94	1:47	1:18.7	1:9.4
Temperature	Quaternary	Per cent Reduction				
20° C.	A	19	13	53	71	99.3
	B	0	28	49	91	99.9
	C	0	0	49	92	99.6
	D	41	50	60	88	99.9
	E	33	66	74	91	99.6
45° C.	A	39	49	67	91	99.9
	B	33	47	78	99.4	99.9
	C	56	51	80	99.5	99.9
	D	44	69	78	99.2	99.9
	E	30	67	89	98	99.9

*The chemical-dry fabric ratios are mathematical calculations of the actual dilutions used.

A further comparison of the bacteriostatic and sanitizing properties of these same quaternaries reveals that 1:5,000 to 1:10,000 dilutions at 20° C. for ten minutes rendered the test fabric bacteriostatic for sixteen hours, whereas a 1:5,000 dilution applied at 20° C. for fifteen minutes produced sanitization, according to the selected end point, only with quaternaries B and D, although the reductions observed with quaternaries A, C, and E closely approached the desired level. Such data indicate a fairly close correlation between the concentrations necessary to secure practical sanitizing action and residual bacteriostatic effects when ap-

plications are made at relatively low temperatures.

On the other hand, for fabric treated for ten minutes at 20° C. and 45° C. to remain bacteriostatic for twenty-four hours or more, dilutions ranging from 1:1,000 through 1:4,000 were found necessary. Thus, if prolonged bacteriostatic effects are desired, it would appear that concentrations considerably higher than those required for sanitizing would have to be employed in treating fabrics.

Insofar as the sanitizing capacity of these quaternaries is concerned, these results seem to confirm the findings reported by Lawrence which showed that a 1:5,000 dilution of alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride was useful for this purpose. This sanitizing value seems, however, to be possessed by the other four compounds as well, provided time and temperature of treatment are adequate.

Mack and associates,[4] on the other hand, concluded that the use of bacteriostatic agents does not reduce total bacterial counts of *E. coli*. The findings herein reported have demonstrated that quaternary ammonium compounds do reduce total counts of *E. coli* in fabrics provided they are employed at suitable concentrations. Also, these reductions were considered to be of a magnitude sufficient to warrant claims of sanitizing value when the chemicals were properly applied, although at dilutions of 1:5,000 and above they did fall somewhat short of the end point which would be required to provide presumptive evidence of disinfection or a treatment that could be considered adequate for fabrics known to carry or strongly suspected of carrying infectious material.

CONCLUSIONS

As judged by their ability to reduce by 99.9 per cent the *E. coli* count in rinse waters of experimentally contaminated fabrics over control rinse waters, the five quaternaries studied appear to have potential value as sanitizing agents in ordinary laundry operations.

The efficiency of all five quaternaries in reducing the *E. coli* count of fabric rinse waters has been shown to depend upon the concentration of the chemical (related possibly to fabric-chemical ratio) and temperature of application.

All five quaternaries, (A) para diisobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride, (B) alkyl (C_8-C_{18}) dimethyl benzyl ammonium chloride, (C) alkyl (C_6-C_{12}) naphthyl methyl pyridinium chloride, (D) dodecyl acetamido dimethyl benzyl ammonium chloride, and (E) cetyl trimethyl ammonium bromide, when applied at 45° C. for fifteen minutes in a dilution of 1:5,000 or at 1 oz. quaternary to 9.4 lb. of dry fabric, reduced by 99.9 per cent the *E. coli* count of the subsequent experimental neutralizer rinse over controls.

At 20° C. with fifteen minutes' exposure, all five quaternaries reduced the *E. coli* count of the experimental rinses by more than 99 per cent.

A reduction of 100 per cent was not secured in the *E. coli* count of rinse waters with any of the five quaternaries studied at dilutions of 1:5,000 and above at either 20° or 45° C. Thus, the potential sanitizing values noted cannot be considered as presumptive evidence of complete germicidal action which would be essential to indicate value for use in disinfection.

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Erratum

In the article by Dr. B. B. Breese, "Aureomycin in the Treatment of Beta Hemolytic Streptococcal Infections," in the January, 1952, issue, the first sentence under Aureomycin Dosage on page 86 should read:

The initial dose given was *20* mg. per kilogram of body weight in twenty-four hours and calculated to the nearest 50 mg.

INFANTILE CORTICAL HYPEROSTOSIS

Report of a Case Responding to Treatment With Corticotropin

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THIS case of infantile cortical hyperostosis is reported because of a good response to treatment with corticotropin.

Infantile cortical hyperostosis is a disease of unknown etiology characterized by an hyperplasia of the cortex or periostium of multiple bones, sometimes with an inflammatory reaction of the overlying tissue, and a generalized reaction. Fifty cases have been reported.

There have been various conjectures as to the etiology. An infectious agent has been considered, either virus or bacterial. Cultures of staphylococcus have been obtained in fluid aspirated from the involved areas or from the throat.[1, 2, 3] Caffey[4] obtained only sterile fluid on aspiration. Rarely and associates[5] considered allergy as a possible etiological factor and obtained a family history of allergies in three of their four cases. In all cases, scurvy, syphilis, vitamin A poisoning, osteomyelitis, and malignancy were ruled out.

The age of onset has usually been near the third month, but one case has been recorded at ten days[6] and several cases have been described during the second year.[7] Those cases occurring near the third month have usually shown involvement of the mandible. Other bones involved have been the tubular bones, scapulae, calvarium, ilium, and ribs. Although lesions of the metatarsals have been noted, none is reported in the metacarpals. In lesions of the ribs, there has been concurrent pleurisy with exudate in several cases.[7] Fever has been present in many cases.

Laboratory studies have shown anemia, leukocytosis with either an increase in lymphocytes or polymorphonuclear cells, an elevated alkaline serum phosphatase, and an elevated sedimentation rate.

Duration has been two to twelve months with eventual complete recovery. Treatment heretofore has made little if any change in the natural progress of the disease. Elimination diets and antihistamines have had no effect on these children. Chemotherapy and antibiotics have been of no aid. One child showed improvement after a cast had been applied to the affected arm for one month.[7]

CASE REPORT

D. B., a white male, was first seen at the age of 4 months with pallor, fever, extreme irritability, and swelling of the right cheek of two weeks' duration.

Both the mother and father were 41 years old and in good health at the time of the child's birth. The mother's pregnancy and the birth of the child were uneventful. The child weighed 9 pounds 2 ounces. He had been in good health before the illness, and he had received an evaporated milk formula with adequate vitamin intake and other foods, although he had not taken orange juice.

At the age of 4 months the child became irritable, took feedings poorly, developed a swelling of the right cheek, and showed daily temperature rises to 102° F. rectally. For a short period there was an area of swelling over the left clavicle which left spontaneously. For one week he received both penicillin and aureomycin without improvement and was then admitted to the hospital for observation, where he

The corticotropin for this case was provided through the courtesy of Dr. Harley E. Cluxton, Jr., Medical Director, The Armour Laboratories.

received both penicillin and dihydrostreptomycin for five days without benefit. During this period swelling appeared in the other cheek and a tentative diagnosis of infantile cortical hyperostosis was made. As x-ray and laboratory studies were not yet conclusive, the child was discharged and observed.

During the following month the child became increasingly ill. The swelling of both buccal areas became more tender and so pronounced that it protruded into the oral cavity and interfered with bending the head forward. For a period he showed actual weight loss and at the end of the month he had gained but two ounces. It then became possible to make a definite diagnosis of infantile cortical hyperostosis and he was admitted to the hospital for trial therapy with corticotropin.

Fig. 1.—Showing facial appearance of patient.

Laboratory Studies.—The alkaline serum phosphatase rose from 6.7 Bodansky units on the first admission to 12.6 units on the second admission. The sedimentation rate was 63 mm. per hour (Wintrobe) on the first admission and remained high during the entire month. The red cell count dropped from 4.76 to 3.92 million and the hemoglobin from 12 to 11.9 grams. The white count on the first admission was 15,000 with 1 basophile, 3 myelocytes, 2 juveniles, 2 stabs, 38 segmentals, 53 lymphocytes, 1 monocyte. Several promyelocytes were seen. The white count varied little during this month. The tuberculin and Kahn tests were negative, the Kolmer anticomplementary. The predominant organism grown on throat culture was *Streptococcus viridans.*

X-ray Studies.—Examination on Aug. 15, 1951, showed marked cortical hyperplasia involving both sides of the mandible, most marked just anterior to the angles. The great soft tissue swelling was also evident. In checking earlier films, an indistinct outline of cortical hyperplasia could be seen which had previously been interpreted as soft tissue shadow. Films of the remainder of the skeleton showed cortical hyperostosis involving the distal two-thirds of the shaft of the left ulna. Films made at the completion of therapy and one month later showed no changes in the lesions, although there was great clinical improvement.

Treatment and Results.—Corticotropin was used in the following dosages: 10 mg. every six hours for twenty-four doses, 5 mg. every six hours for twenty-four doses, 5 mg. every twelve hours for four doses, and then 5 mg. every twenty-four hours for three doses.

Forty-eight hours after onset of treatment the child's temperature, which had been showing daily rises to 102° F., dropped to normal and has since remained normal. The swelling of the face left rapidly; his appetite improved remarkably. During the

first ten days he gained 12 ounces and has continued to gain at a normal rate. He smiled for the first time since the onset of his illness and sat up for the first time. His sedimentation rate which had been at about 60 mm. per hour dropped at a regular rate and was normal three weeks after completion of his course of treatment. The alkaline serum phosphatase dropped to 8.4 Bodansky units one month after completion of treatment. The x-rays, however, showed practically no change. He did not receive vitamin supplements during the early part of this period of recovery. Four months after completion of treatment he was still well.

Fig. 2.—View of mandible showing hyperostosis.

Fig. 3.—Left forearm showing ulna with subperiosteal formation.

DISCUSSION

The mode of action by which corticotropin caused improvement in this illness is not known since the etiology of the disease is not known. The return of the temperature to normal so

promptly may not have been due to any specific action of the corticotropin in this disease, since an antipyretic action has been noted in many other conditions. Although there is a spontaneous improvement in infantile cortical hyperostosis, the prompt improvement with treatment was almost certainly not circumstantial. Improvement may have followed an altered antigen-antibody response. Caffey has pointed out that the lesions in this condition resemble those of rheumatoid arthritis, and it may be that the hormone causes a similar response in both diseases. Corticotropin may affect calcium metabolism to cause an osteoporosis. That this factor is of no importance is shown by the clinical improvement preceding any bone changes.

SUMMARY

1. A case of infantile cortical hyperostosis in a 4-month-old child is reported, with involvement of the mandible and left ulna.

2. Following the administration of corticotropin there was a rapid improvement in clinical signs, with later return of the laboratory studies to normal. X-rays of the involved bones showed no changes in the lesions one month after treatment, but were normal four months after treatment.

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DUPLICATION OF THE STOMACH

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A CASE of pyloric obstruction secondary to partial duplication of the stomach is presented because of the rarity of duplication of this part of the gastrointestinal tract and its unusual manifestation in this case.

Ladd and Gross[1] report only one case of duplication of the stomach in their series of eighteen duplications of the gastrointestinal tract.

CASE REPORT

A 2-year-old white male was admitted to Louisville General Hospital with fever, vomiting, and lethargy. One week before admission the patient had had a mild upper respiratory tract infection. Four days prior to admission he became lethargic and vomited. The next day he felt somewhat better, had a bowel movement and ate well. That evening he again vomited and continued to do this for three days, during which time he had no bowel movements. One day prior to admission he was seen in the Pediatric Clinic where a diagnosis of tonsillitis and acute otitis was made and he was treated with antibiotics. On return to the clinic the next day he was markedly dehydrated and was admitted to the hospital.

The past history revealed he was born at this hospital after a nine-month normal pregnancy. Delivery was uncomplicated. The newborn record contained a note stating that the patient had a cauliflower type deformity of his ears, and because of a faint heart murmur was thought to have congenital heart disease. During the following two years he was seen frequently in the Pediatric Clinic, but the diagnosis of congenital heart disease was not confirmed. His clinic visits were chiefly for allergic eczema and draining ears. He had had no other illnesses except German measles at the age of 12 months. His growth was somewhat retarded.

A careful feeding history revealed no previous difficulties; the child had always eaten well. A history of vomiting in infancy could not be obtained. Pica was denied by the mother.

Physical examination revealed a poorly nourished and only fairly well-developed, acutely ill 2-year-old white male, markedly lethargic but able to respond to painful stimuli. The pulse was 120, respirations 40 per minute, and the temperature was 101.6° F. The head was normal in contour, with the anterior fontanel admitting the tip of one finger, although the inner table was closed. The eyes showed slight conjunctival injection. The fundi appeared normal. The external ears were malformed. The right eardrum was scarred and contained a central perforation from which there was moderate drainage. The posterior pharyngeal wall was moderately injected. A few shot-sized anterior cervical nodes were noted. Expansion of the thorax was equal bilaterally. Percussion of the lungs was negative, and on auscultation a few coarse râles were heard. The size of the heart was within normal limits. The rhythm was regular, and no murmurs were heard. The abdomen was scaphoid and soft. A soft elastic mass could be palpated in the epigastrium. On continued palpation this mass appeared to become firmer, and a peristaltic wave was observed through the overlying skin. The liver could not be felt. The tip of the spleen was barely palpable at the costal margin. On rectal examination fecal material was found in the ampulla. There was no blood on the examining finger. The genitalia were those of a normal male infant. Extremities showed underdeveloped, somewhat atrophic muscles. The

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joints were broad, especially in the knees, and the movements were free. Complete neurological examination revealed nothing of note, except hypoactive reflexes. There were small areas of eczema below both ears.

tive except for 1 plus acetone. The blood CO_2 content was 26.7 meq. per liter and the blood pH was 7.61.

A flat roentgenogram of the abdomen in both the recumbent and upright positions demonstrated a consid-

Fig. 1.

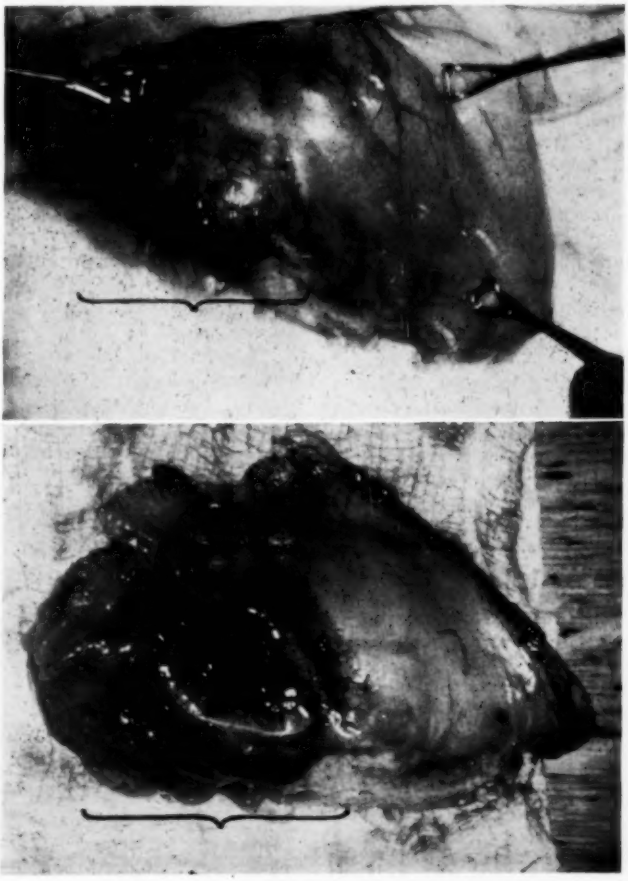

Fig. 2.

Fig. 1.—The intact stomach at time of operation. The duplicated portion is indicated.
Fig. 2.—The resected specimen. The opened duplicated stomach is indicated.

Blood count on admission showed 5,480,000 red blood cells per cubic millimeter, 13½ grams of hemoglobin, and a white count of 19,200 with 78 polymorphonucleocytes and 22 lymphocytes. Urinalysis was essentially negative except for 1 plus acetone. The blood CO_2 content was 26.7 meq. per liter and the blood pH was 7.61.

A flat roentgenogram of the abdomen in both the recumbent and upright positions demonstrated a considerable amount of gas and fecal material throughout the colon and in a few loops of small bowel. Except for a small air bubble in the extreme upper portion of the fundus, the stomach was filled with fluid.

Intravenous fluid replacement therapy was immediately started. During the next twelve hours his condition deteriorated while he continued to vomit. At this point he also had a generalized convulsion lasting forty to fifty seconds. Calcium gluconate was added to the intravenous fluids, and gastrointestinal suction was instituted. Blood total protein was 4.1 grams per cent, chlorides 76 meq., a CO_2 of 27.8 meq. per liter and pH 7.66, phosphorus 1.46 meq. per liter.

An electrocardiogram showed a heart rate of 100 with regular sinus rhythm, P-R interval .12, Q-S interval .02, Q-T interval .4 second. Changes consistent with the diagnosis of hypokalemia were noted.

During the next five hours the patient's condition gradually improved and hydration seemed to be considerably better.

Chemical and microscopic examinations of the spinal fluid were reported as normal.

The diagnosis of hypertrophic pyloric stenosis was considered. Approximately twenty-four hours after admission the patient was transferred to the surgical department. At this time the vomitus became blood tinged leading to the fear of overlooked upper gastrointestinal tract strangulation. This prompted immediate surgical intervention.

Operative Procedure.—A right upper abdominal paramedian incision was made. Exploration of the contents of the abdominal cavity revealed a mass near the pylorus. This mass was firm, rubbery in consistency, and was situated at the distal third of the stomach and pylorus down to the duodenum on the anterior wall of the stomach. (Fig. 1.) There was no involvement of adjacent organs.

A small incision was made into the mass and approximately 15 c.c. of green viscous fluid were evacuated. (Fig. 2.) At this point the lesion was recognized as a duplication of the stomach, since the mucosa lining the cavity was similar to that of gastric mucosa. Finger palpation could not locate any communication between the duplication and the true stomach. The contents of the closed duplication had apparently created enough pressure to cause it to bulge into the pyloric portion of the true stomach and occlude its lumen. As soon as the fluid was evacuated, the lumen of the true stomach reopened. Because of the common wall between the posterior wall of the duplicated stomach and the anterior wall of the true stomach, it was decided that a subtotal gastric resection was the preferred treatment.

The distal third of the stomach was resected and a retrocolic Pólya anastomosis was performed using an inner row of continuous catgut suture, and an outer row of 4-0 silk Lembert sutures.

Examination of the remainder of the gastrointestinal tract was then done. No other abnormalities could be found.

The histological sections revealed a common muscular wall between the true stomach and the duplication. Both had intact gastric mucosal surfaces. No communication could be located.

Postoperative Course.—The child had a totally uneventful postoperative course. Repeated blood counts up to six months have failed to reveal any evidence of anemia.

SUMMARY

A case of duplication of the stomach is reported. The presenting findings were those of high intestinal obstruction with vomiting, marked dehydration, and a palpable epigastric mass. Resection of the distal one-third of the stomach including the duplication was carried out. The recovery was uneventful.

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A CASE OF PERFORATED GASTRIC ULCER MANIFESTED BY HEMATEMESIS IN AN 8-WEEK-OLD INFANT

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IT IS the purpose of this paper to present a case of perforated gastric ulcer in a 2-month-old infant in whom the cardinal symptom was hematemesis.

Perforated ulcer is by no means unknown in pediatric literature, but occurs so infrequently that it is not usually considered in the differential diagnosis of the acute abdomen in infancy.

The presence of peptic ulcers in infancy was first reported in the early part of the nineteenth century by Cruveheiler,[4] who found multiple gastric ulcers at post-mortem examination of three infants, aged 1, 2, and 4 weeks, respectively.

In 1913, Holt[1] reviewed ninety-one cases reported in the literature up to that time. A study of the literature by Bird, Limper, and Mayer[5] in 1941 uncovered 243 additional cases. Two more cases were reported in 1950 by Plummer and Stabins[7] and still another by Wright and Scott.[3] In September, 1951, Kellogg and associates[8] reported the only known survival of a newborn infant with a perforated gastric ulcer.

The etiology and pathogenesis of infantile peptic ulcer is not known. Guthrie[2] postulates that circulatory instability, especially as produced by prolonged labor, tends to devitalize the gastric and duodenal mucosa. Cole[6] found ulcers reported in conjunction with certain other pathological states frequently enough to suggest a causal relationship. Some of the conditions he cites in this connection are:

a. Bacteremias and suppurative or tuberculous meningitis.

b. Burns and scalds (Curling's ulcer).

c. Direct epigastric trauma.

d. Nonspecific gastritis.

e. Anoxia of mucosa due to asphyxia, hyperperistalsis, cerebral disease or hemorrhagic disease of the newborn infant.

The symptomatology presented by infants with a perforated ulcer varies considerably. Almost all of the patients present a picture of shock and collapse. Cole[6] states that in the first fourteen days of life the outstanding symptoms are hematemesis or melena, while in the older infant shock, vomiting, or peritonitis may occur first with no blood evident in vomitus or stool. He reports the case of a 9-week-old infant whose clinical picture was entirely compatible with a diagnosis of hypertrophic pyloric stenosis, even to the presence of a palpable tumor mass in the epigastrium and visible peristaltic waves. At post mortem these proved to be the result of pyloric obstruction due to hemorrhage around a perforated prepyloric ulcer. The 1-day-old infant of Wright and Scott[3] presented no physical findings other than cyanosis and tachycardia until the fifth day of illness, when a clinical peritonitis was evident. It might be questioned whether this patient had a perforated ulcer since the first day or whether this developed as a result of local anoxia due to some other cause. At post mortem there was, however, no pathology found other than a gastric perforation.

The prognosis in this condition is extremely grave, mortality being reported as well over 90 per cent.[6] The only patients reported as surviving were those subjected to prompt surgery.[7, 8]

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CASE REPORT

S. S., an 8-week-old white male infant, entered the hospital with a three-hour history of grunting and whining and a one-hour history of several episodes of vomiting of bright red liquid blood. The estimated blood loss was one-half cup. All other symptoms were denied by the mother. The infant was a full-term 6 pound 6 ounce infant in good health. Difficult labor, neonatal cyanosis, and any previous illnesses were denied. The infant was entirely well until the acute onset of the present illness. His diet consisted only of an evaporated milk formula and a standard multivitamin preparation.

Physical examination revealed a well-developed, well-nourished infant male in profound shock. The skin was pale, cold, and moist, the respirations shallow and labored, and the pulse rapid and thready. A bright red bloody froth emanated from the mouth and nose. The heart was rapid. There were coarse rhonchi throughout both lung fields. The abdomen was markedly distended with boardlike rigidity. It was impossible to evaluate tenderness. No masses could be palpated and no peristaltic sounds could be heard. The hemoglobin was 10.0 grams and the white blood count 10,000 with a normal differential count.

A flat plate of the abdomen revealed a large area of translucency in the mid-epigastrium, consistent with distended stomach or a loop of bowel under tension. No free air was noted.

It was felt that the patient's condition was too critical to permit surgical intervention. Emergency measures, such as blood transfusion, antibiotics, continuous gastric suction, Adrenalin, and oxygen, were started and continued for several hours, but the patient never recovered sufficiently to permit surgical procedure and expired twelve hours after admission to the hospital after a fifteen-hour illness.

Post-mortem examination revealed a large amount of fluid and milk in the peritoneal cavity, with a marked peritoneal inflammatory reaction. There was a 1 × 1 cm. perforation on the greater curvature of the fundus of the stomach. The remainder of the examination, including the brain, was essentially normal.

SUMMARY AND CONCLUSIONS

A case of perforated gastric ulcer manifested by hematemesis in an 8-week-old infant has been presented. In this case the physical findings of abdominal distention with boardlike rigidity and the absence of peristaltic sounds pointed to the presence of a perforated viscus with a generalized peritonitis. Despite intensive therapy, the patient never recovered from shock sufficiently to make surgical intervention feasible.

It is evident that perforated gastric ulcer must always be considered in the differential diagnosis of the acute abdomen in infancy, as well as in cases of unexplained shock and collapse. It would seem that surgical intervention offers the only hope of cure and should be carried out without delay whenever possible.

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AN IMPROVED EXAMINING PAD FOR INFANTS

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THE crying of small infants before, during, and after examination in the pediatric office has been found to be largely eliminated by the use of an examining pad which tends to support the baby, prevent rolling from side to side, and assists the nurse in holding the infant in the proper attitude for examination by the physician.

The pad is constructed of foam latex on a light plyboard base and is completely covered with plastic material, taking care that none of the seams are on the upper surface preventing penetration of the plastic cover by urine or feces.

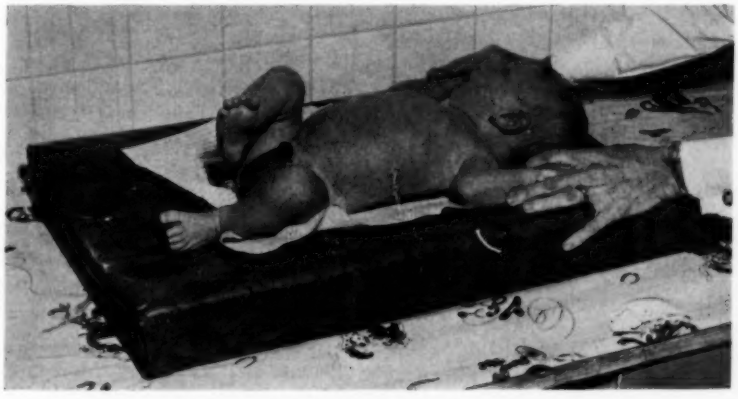

Fig. 1.

The over-all dimensions of the pad are 24 by 16 inches, with the longer sides built up three inches forming a lengthwise depression roughly the width of the infant's shoulders and buttocks. The surface upon which the infant lies is concave and his shoulders and buttocks are so cradled that rolling is discouraged and the infant is comfortably supported.

In construction, the plyboard base is first covered with a layer of one-inch latex and the sides are built up with narrow strips of the same material, beveled so the sides slope gradually to the center flat surface which is six inches wide. This is then covered over all with plastic material of the finest grain to facilitate easy cleaning. The plastic material can be secured in any color to blend with the other furnishings of the office. The pad can be easily and economically made by any experienced upholsterer. Individual paper towels are used to cover the pad during use. The unavoidable urine and feces accumulate in the depression and are easily wiped away.

Because of the lightness of the pad it can be placed on a regular examining table for the smaller patients or removed if larger children are to be examined.

Symposium on Cerebral Palsy
Part I

OBSTETRICAL FACTORS IN CEREBRAL PALSY

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THE hazards of the birth processes and obstetric procedures on the fetus and newborn infant are fully appreciated by all obstetricians. Neurological sequelae, such as cerebral palsy, mental retardation, epilepsy, and many behavior problems and other ill-defined conditions have been charged to the birth act since the time of Little. In spite of the knowledge accumulated in the past century there has been no consistent opinion as to the nature of these processes and the exact factors which may be responsible. Oversimplification of the birth process has led to improper deductions in the past to produce a literature with amazing extremes and divergence of opinion. Obstetrical factors such as the role of forceps, breech delivery, analgesia and anesthesia, in the production of "birth injury" and "anoxia," in relationship to the problem of cerebral palsy have been extremely controversial. In recent years obstetricians have not entered into this debate, not purposely, but because they have been busy with other problems of their medical specialty. It is necessary therefore to point out some of the aims and present difficulties of the obstetrician and their possible relation to cerebral palsy. Eastman defines the aims of modern obstetrics, in general, to have every pregnancy culminate in a healthy mother and healthy baby. In addition, the role of the modern obstetrician has had a threefold mission and purpose. First, to reduce maternal mortality to its irreducible minimum. Second, to reduce fetal and neonatal mortality, and finally, to safeguard the whole course of pregnancy, labor, and the puerperium, so that both mother and child conclude the experience in the optimum physical and mental state of health.

In regard to the maternal mortality problem modern obstetrics has had an important part so that in the past thirty-five years, the national maternal mortality rate has decreased from 60 to 90 deaths per 10,000 live births in 1915 to approximately 10 to 15 deaths per 10,000 live births in the United States in 1950. In numerous all-white private clinics this figure approaches 0 to 5 deaths per 10,000 live births. This dramatic drop has been attributed to numerous factors and agencies, but the most important may be summarized as follows:

1. Widespread training and education in obstetrics.
2. Agencies for the creation of prenatal maternal care on city, state, and national basis.
3. Blood banks, chemotherapy, and adequate personnel.
4. Increase in hospital deliveries.
5. Maternal mortality committees.

The reduction of stillbirths and neonatal deaths in the United States has been progressively better; however,

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much improvement can be expected in the future. It is this fetal wastage that has occupied the obstetrician in the past decade. It is to this problem that most of his efforts and research have been expended. For instance, the stillbirth rate for fetuses born at five months or more of gestation in the United States was 239 per 10,000 live births in 1945, having dropped from 394 per 10,000 live births in 1922. Neonatal deaths in the first month of life have declined from 444 deaths per 10,000 live births in 1915 to 243 deaths per 10,000 live births in 1945. However, there has been a plateau in these statistics during the past four or five years. The problem of obstetrics in the United States may be summed up briefly as follows in the year 1946:

Maternal deaths	5,153
Stillbirths	74,849
Neonatal deaths	79,079

Many people, such as Potter, who have analyzed these statistics feel that any condition which affects any one of the above causes of deaths will affect them all. Only by a combined study of the factors of one can the reduction of the others take place.

The discussion to follow will attempt to cover only three broad topics in the vast subject of obstetrical factors in cerebral palsy. First, a review of the literature will be presented. Second, the causes of fetal and neonatal deaths will be briefly tabulated in order to demonstrate the similarities between factors producing lethal injury and those factors associated with cerebral palsy which may be assumed to be sublethal injury. And finally, a portion of the problems that should be investigated in order to improve obstetrical knowledge regarding the effect of the birth processes and obstetrics procedures upon the newborn infant.

REVIEW OF THE LITERATURE ON OBSTETRICAL FACTORS IN CEREBRAL PALSY

It is obvious that I must be brief and arbitrary in presenting as large a subject as this title would include. The literature on this subject begins with the paper by Little entitled "On the Nature and Treatment of Deformities of the Human Frame," published in 1853. In this treatise, Little described four cases of "spasmodic affection" which occurred due to difficulty and slowness of parturition, in which the babies were asphyxiated and demanded resuscitation for several hours following birth. In 1862 Little wrote further on this disease, and his article was entitled "On the Influence of Abnormal Parturition, Difficult Labors, Premature Births, and Asphyxia Neonatorum on the Mental and Physical Condition of the Child Especially in Relation to Deformities." Over the next one hundred years as illustrated in Table I the causes of cerebral palsy varied from Little's concept to those of McNutt who felt that meningeal hemorrhage was the predominant cause. Even medical masters such as Sigmund Freud and William Osler delved into this field. Freud thought it was an intrauterine disease; Osler studied seventeen cases and found porencephalic cavities, diffuse sclerosis, and atrophy as a consequence of intracranial hemorrhage at birth. In 1938 the possibility that excessive sedation of the mother during labor might be the cause of neonatal asphyxia was advanced by Schreiber. Schreiber also suggested that some of the cere-

bral lesions considered as congenital commonly due to atrophic lobar sclerosis, developmental defects, and to a lesser extent due to birth injury.

Benda in a study of mentally defective children found that practically all modes of birth contributed to birth injuries and that cerebral hemorrhage was responsible for many cases of defective children. Thus, Table I is not a complete bibliography and does not intend to go into the problem of the intimate differences of opinion. More complete discussions on the etiology of cerebral palsy are to be found in the papers of Wolf, Ford, Benda, Phelps, and Perlstein.

The remainder of this review of the literature will be devoted to a few clinical papers on studies concerned with the birth processes and the future development of cerebral palsy. In most of these papers information was secured in retrograde questioning of the parents. Attempts to find the birth record five and ten years after might also be sequelae of oxygen want. In 1941 Penfield and Erickson in a study of epilepsy and cerebral localization postulated that birth ischemia could form local microgyria and brain cysts due to arterial occlusion. In the same year Friedman and Courville demonstrated that "atrophic lobar sclerosis" and partial cerebral agenesis was a focal or diffuse necrosis of the cerebral cortex and that these conditions were a sequelae of neonatal asphyxia. Courville has been the leading advocate of this general concept, and in subsequent papers has continued to advance the idea that a variety of lesions responsible for idiopathic infantile diplegias, idiocies, and epilepsies of indefinite etiology are caused at least to a considerable extent by neonatal asphyxia. Another opinion was voiced by Ford, who, writing as early as 1927, and again in 1944, felt that meningeal hemorrhage and thrombosis of the superior longitudinal sinus was an infrequent cause

TABLE I. HISTORICAL ASPECTS AS TO OBSTETRICAL CAUSES OF CEREBRAL PALSY

AUTHOR	YEAR	POSSIBLE CAUSE
1. Little	1853, 1862	Influence of abnormal parturition, difficult labors, premature birth asphyxia neonatorum.
2. McNutt	1885	Meningeal hemorrhage.
3. Freud	1897	Intrauterine disease.
4. Osler	1889	Intracranial hemorrhage.
5. Guthrie	1913	Association of kernicterus with choreiform movement.
6. Collier	1924	Pulmonary degeneration of neurones to unknown causes.
7. Yannet and Zimmerman	1935	Relation of icterus and cerebral sequelae.
8. Alpers and Marcovitz	1938	Birth injury may produce palsy.
9. Schreiber	1938	Cerebral lesions considered congenital may be due to asphyxia.
10. Penfield and Erickson	1941	Certain lesions of birth and early infancy capable of producing microgyria and brain cysts.
11. Friedman and Courville	1941	Atrophic lobar sclerosis and partial cerebral agenesis are residuals of asphyxia.
12. Ford	1944	Atrophic lobar sclerosis, developmental defects, and birth injury.
13. Benda	1945	Supports birth injury idea. Symmetrical paralysis may have asymmetrical lesion.

of congenital diplegia but was more its occurrence were often futile. For instance, one of the first papers, that of Gustafson and Garceau, in 1941, reported the obstetrical factors in 185 cases of cerebral palsy as follows:

Place of delivery	12.4% hospital born	
	87.6% born at home	
Age of mother	Not significant	
Parity	57% primiparas	
Sex	58% male	
Length of labor	Less than 1 hour	9 cases
	1- 6 hours	56 cases
	6-12 hours	39 cases
	12-18 hours	19 cases
	18-24 hours	10 cases
	24-48 hours	12 cases
	Unknown	7 cases
Duration of pregnancy	5% postmature	
Type of delivery	35% premature	
	Breech	17 cases (9.7%)
	Face	3 cases
	Vertex	163 cases
Anesthesia and analgesia	No role	
Pituitary extract	13% of cases	
Resuscitation	63% of cases	
Cyanosis	60% of cases	
Convulsions	41% of cases	

This study emphasizes the factors of primiparity, length of labor, prematurity, breech delivery, pituitary extract, asphyxia at birth, cyanosis, and convulsions in the newborn infant as important factors in the birth process in relationship to cerebral palsy. Yannet studied eighty-six cerebral palsy patients in 1944 to determine significant aspects in etiology. His conclusions were as follows:

Age of mother	29.8 years average
Parity	No difference until after third child
Genetic factor	Increase of mental retardation in siblings
Abnormal labor	25% of cases. 50% of hemiplegias
Prematurity	12%
Convulsive disorders	1st year of life
Associated congenital defects	Primarily eye defects

Yannet, however, did not feel that his data regarding the birth processes was satisfactory since the information was often obtained ten to fifteen years after the birth of the child and maternal impressions were often tinged by interim opinions and suggestions. In 1947 McGovern and Yannet made a more detailed clinical analysis of a group of asymmetric spastic cerebral palsy. Their cases were divided into two groups. The group in which a definite history compatible with the diagnosis of birth trauma was present was shown to differ in many respects from the undifferentiated group in which this history was absent. These differences were:

1. High proportion of first born in group with birth trauma.
2. Advanced age of mothers at the time of birth in the undifferentiated group.
3. The smaller average head size in the group which experienced birth trauma.
4. Increased incidence of prematurity in undifferentiated group.
5. Tendency for hemiplegia in the undifferentiated group to involve the right side, while hemiplegia on the left side occurred in practically all cases of palsy due to birth trauma as well as of postinfectious palsy.

These authors concluded that this undifferentiated group which represented 54 per cent of the total number of cases of asymmetric spastic paralysis have many features in common with the spastic diplegias and probably represent the result of prenatal conditions leading to developmental cerebral defects. The definition of birth trauma in the differentiated group depended upon the following criteria:

1. Labor was abnormally long, difficult, or complicated.
2. Immediate postnatal period was stormy:
   a. Delay in initiation of respirations.
   b. Cyanosis.

c. Excessive drowsiness.
d. Convulsions.

Faber in 1947 studying cerebral damage in ninety-nine infants found the following factors to be present:

Prenatal Factors:	*Cases*
Placental separation + placenta previa	15
Toxemia	10
Oversize infant	9
Premature rupture of membranes	5
Maternal trauma (falls, etc.)	5
Rh incompatibility (kernicterus?)	4
Premature labor pains	2
Attempted abortion	2
Cardiac decompensation	2
Maternal infectious disease	6

Paranatal Factors:	*Cases*
Anesthetics	
Nitrous oxide	22
Chloroform	4
Ether	8
Spinal	1
Sedation	
Unspecified shots	5
Pills and barbiturates	5
Sedation heavy	6
Induced labor	
Oxytoxics (pitocin?)	2
Castor oil	1
Quinine	1
Breech presentation	9
Delivery, abnormal	22
Prolonged	7
Dry	4
Version	2
Precipitate	5
Cesarean	3
High forceps	1
Abnormalities of cord	6
Tight cord	4
Prolapse	1
Short	1

Of these, abruptio placentae and placenta previa, toxemia, maternal trauma and disease, Rh incompatibility, breech presentation, abnormal delivery appeared to be increased above the normal incidences in average obstetrics clinics. Included also in these prenatal and paranatal factors in Faber's study were the following postnatal factors:

Postnatal Factors:		*Cases*
Infectious		26
Encephalitis	13	
Measles	4	
Equine	3	
Unspecified	6	
Meningitis		3
Pertussis		5
Pneumonia		3
Laryngeal diphtheria		1
High temperature with convulsions		1
Noninfectious		13
Convulsions severe (cause unknown)	6	
Trauma to head	4	
Intracranial hemorrhage	1	
Prolonged apnea	1	
Apnea and cardiac arrest (from Mecholyl)	1	

Evans in 1948 observed 114 cases of cerebral palsy. He obtained most of the information regarding the obstetrical factors from the mother but was also able to get some help in 80 per cent of the cases from the mother's attendant at birth. In seventeen cases the cause appeared to be:

	Cases
Hydrocephalus	4
Meningitis	1
Nonsuppurative encephalitis	2
Hemorrhagic disease of newborn	2
Kernicterus due to erythroblastosis	8

The remaining ninety-seven cases included thirty-eight of spastic paraplegia or tetraplegia and thirty-eight of double athetosis. In the thirty-eight spastic cases a family history of the disease, parental consanguinity, sex, parental age, birth order, maternal health during pregnancy, and abnormalities of labor did not appear to be important. There was no evidence of infertility, frequent abortion, or frequent twinning in the parents of

these children. Premature birth, however, was very common.

In the athetoid cases similar findings were observed. Prematurity was common but not to the same degree as in the spastic cases. Obstetrical analgesia, forceps deliveries, neonatal asphyxia, convulsions, and difficulty in feeding were also common. These features suggest an association between difficult labor and development of double athetosis. Evans suggested that three lines of approach be followed in the genesis of cerebral palsy:

1. Close clinical and pathological investigation of individual types of cerebral palsy, rather than "Little's disease" in general.

2. Elucidation of the mechanism of damage to the nervous system in conditions in which the cause is known; for example, hydrocephalus, Rhesus incompatibility.

3. Experimental work on the effect of asphyxia and of venous and arterial lesions on the immature central nervous system.

Link in a study of 150 children in Buffalo with cerebral palsy also assessed numerous factors. His data may be summarized as follows:

Average age of mother	24.7 years
Primiparas	53%
Congenital group	19%
Associated epilepsy	20%
Version and extraction	18%
Feeding difficulties	77%
Asphyxia neonatorum	81%
Prematures	15.39%
Breech delivery	12%
Difficult forceps	12%
Syphilis	2%
German measles	0.6%
Encephalitis	0.6%
Hemorrhagic disease	0.6%
Twins	4.0%

Link felt that a high incidence of premature infants and forceps promoted a spastic type of disease while with breeches, version and extraction, and asphyxiation, a high incidence of athetosis was present. He concluded that about 50 per cent of the cases were preventable.

In a study by Asher and Schonell in 400 cases of cerebral palsy observed in England, a closer comparison of the incidence of certain obstetrical factors associated with this entity as compared to the normal incidence of the factor in normal obstetrical cases was made and summarized in Table II. These authors concluded that the incidence of diabetes, primiparity, male infants, prematurity, twins, abnormal labor, forceps, birth injury and asphyxia, neonatal jaundice, Rh incompatibility, and kernicterus were of significantly higher incidence than in the population of England. Athetosis was usually the result of birth injury, asphyxia, or neonatal jaundice. Spastic paralysis was produced by birth injury or genetic and intrauterine factors. There was no evidence in this study that asymmetrical spasticity was more likely to be due to birth injury than symmetrical paralysis.

In a study by Denhoff and Holden in 100 cerebral palsy children in Providence, R. I., itemized in Table III, the maternal factors of nausea and vomiting, hypertension, anemia, and vaginal hemorrhage were greatly increased over the control study. Mid-forceps and breech delivery were the commonest obstetrical factors present. Cyanosis, anemia, and prematurity were common factors in the history of neonatal period. One interesting point in regard to neurological sequelae, was that in thirty-five children with

TABLE II. OBSTETRICAL FACTORS OF CONGENITAL CEREBRAL PALSY
Asher and Schonell (1950) England (400 Cases)

	INCIDENCE CEREBRAL PALSY CASES (%)	NORMAL INCIDENCE (%)
1. Maternal age	Slightly older	
2. Toxemia	7.4	8.0
3. Diabetes	0.8	0.1
4. Primiparas	56.4	47.0
5. Sex		
Male	57.0	51.3
Female	43.0	48.7
6. Prematurity	39.4	5.0
7. Twins	5.4	1.2
8. Abnormal labor	39.0	
9. Forceps	24.0	5.0
10. Birth injury and asphyxia	38.0	
11. Neonatal jaundice	10.0	
12. Rh incompatibility	12.0 Rh-	8.2
13. Syphilis	0	1.0
14. Kernicterus	5.6	

TABLE III. EVALUATION OF CAUSATIVE FACTORS IN 100 CASES OF CEREBRAL PALSY
Denhoff and Holden (1951)
Meeting Street School for Cerebral Palsy Children, Providence, R. I.

	NO. AND % WITH C.P. CHILD (100 CHILDREN)	% CONTROLS (504 BIRTHS)
Pregnancy Disorders		
Nausea and vomiting	23	0.6
Hypertension	14	0.8
Anemia	12	0.4
Vaginal hemorrhage	12	0.4
Obstetrical Complications		
Midforceps delivery	16	3.1
Breech delivery	9	0.6
Birth-Neonatal History		
Required oxygen at birth	30	0.8
Required transfusion	7	0.2
Prematurity	30	2.0
Cyanosis	28	1.6
Listlessness	8	0.2
Hypertonicity	5	1.6

symptoms suggesting brain damage in the control series no case of cerebral palsy has been uncovered at the end of a one-year period. A number of other factors were present in the Denhoff and Holden study and listed as follows:

Neonatal convulsions	10%
High forceps	5%
Prolonged labor	10%
Precipitate delivery	5%

Numerous other obstetrical factors were present in the palsy cases but they were not elicited in suitable control material for comparison.

One of the most recent studies is that of McKhann, Belnap, and Beck, who studied 419 children with mental retardation, convulsive disorders, and cerebral palsy. Their data is in tabulated form in Table IV. These authors stress such factors as abruptio placenta previa, kernicterus, prematurity, oversized infant, toxemia, maternal illness, prolonged labor, heavy sedation, induced labor, etc.

However, in the third column under "clinic incidence" data have been recorded which might alter the importance of some of their data. Nevertheless, this study tends to show what a significant role the birth processes and prenatal influences have on the future development of neurological sequelae.

TABLE IV. STUDY OF LATE EFFECTS OF CEREBRAL BIRTH INJURY
McKhann, Belnap, and Beck, Cleveland (1951)
419 Children With Mental Retardation, Convulsive Disorders, and Palsy

	NO. OF CASES	% OF TOTAL	HOPKINS CLINIC INCIDENCE (%)
Etiology			
Birth injury (prenatal and paranatal)	218	53.0	
Hereditary disease + postnatal	17	4.1	
Congenital defects and developmental anomalies	13	3.2	
Mongolism	24	5.8	
Postnatal injury	57	13.8	
Unknown	76	18.4	
Kernicterus	7	1.7	
Causes in Prenatal Period			
Premature separation of placenta	7	4.0	1.5
Placenta previa	5	3.0	0.5
Kernicterus	7	4.0	
Prematurity	27	15.7	11.0
Oversized infant (over 3,800 grams)	6	3.5	
Toxemia	0	5.0	11.0
Maternal illness (anoxia)	6	3.5	
Causes in Paranatal Period			
Prolonged labor	7	4.0	5.0
Prolonged and heavy sedation	10	6.0	
Marked sedation	19	11.0	
Induced labor	5	3.0	4.0
Breech delivery	7	4.0	4.3
Cesarean section	14	8.0	6.0
Cord defects			
Prolapse	2	1.0	0.4
Holding back head	17	10.0	
Tight about neck	9	5.0	5-10
High forceps	5	3.0	0.0
Precipitous delivery	9	5.0	6.0

In one of the largest studies, Lilienfeld and Parkhurst reviewed the association of certain factors of pregnancy and parturition and the development of 561 cases of cerebral palsy from the Crippled Children's Program of the New York State Department of Health. Their data was obtained from birth certificates in that state, in which the complications of pregnancy, labor, and birth weight have been voluntarily reported by physicians since 1940. The children in their study were born during the period 1940 to 1947. Thirty-eight per cent of the cerebral palsy patients had one or more complications as compared with a prevalence of 21 per cent of all births. With regard to specific complications, the data suggested that those complications which resulted in higher combined infant loss rates also had a higher degree of association with the development of cerebral palsy. In addition, those complications which are more commonly associated with fetal anoxia had a higher degree of

association than those more prone to produce mechanical birth trauma. The relationship of various obstetrical operative procedures to cerebral palsy was not borne out by the data after association of complications with operative procedures was taken into consideration. Prematurity was associated with cerebral palsy. This was true both when prematurity resulted from definite complications and when the cause of the prematurity was unknown. The maternal age-birth order distribution among the cerebral palsy cases was suggestive of the existence of the same distribution that prevails among combined infant loss. Lilienfeld and Parkhurst then developed a unique point from their data. The mothers of the children with cerebral palsy had approximately 35 per cent more infant loss in pregnancies previous to the birth of the cerebral palsy case than in the population in general.

The association of several factors of pregnancy and parturition with the development of cerebral palsy was of a pattern similar to that prevailing in combined infant loss. These authors suggest a postulation of the existence of a "continuum of reproductive wastage" with a lethal component consisting of abortions, stillbirths and neonatal deaths, and a sublethal component consisting of cerebral palsy and other related conditions.

From the review of the literature it is apparent that a large number of factors in the prenatal, paranatal, and postnatal period play a role in etiology of cerebral palsy. Although these studies are incomplete and much improvement is needed, it is apparent that the following factors play some role:

Prenatal Factors in Cerebral Palsy:	*% of Cases*
Maternal trauma	5
Maternal disease	6
Nausea and vomiting	23
Hypertension	14
Anemia	12
Vaginal hemorrhage	12
Premature separation of placenta	(4-15)
Placenta previa	3
Primiparity	57
Toxemia	(5-10)
Diabetes	0.8
Paranatal Factors:	
Forceps	24
Midforceps	16
High forceps	(3-5)
Breech	(4-9)
Version and extraction	18
Cesarean section	(3-8)
Holding head back	10
Precipitate delivery	5
Pituitrin stimulation	13
Child Factors:	
Twins	5
Sex	57 male
Kernicterus	(4-6)
Neonatal jaundice	10
Rh incompatibility	12
Cyanosis	30-70
Required oxygen	30
Birth injury and asphyxia	38-53
Convulsions	10-30

The above list of obstetrical factors in cerebral palsy are at first glance impressive but considerable difficulties are encountered in interpretation and in definition.

ANALOGY OF STUDIES OF THE ETIOLOGY OF FETAL AND NEONATAL MORTALITY AND CEREBRAL PALSY

Any student of the causes of fetal and neonatal death would be attracted to the similarities of the obstetrical factors involved in the etiology of cerebral palsy and his own difficult problem. It might therefore be profitable to analyze the problem of fetal and neonatal death in order to gain

insight into the obstetrical factors producing lethal injury as compared to sublethal injury which might be related to the problem of the etiology of cerebral palsy.

Lilienfeld and Parkhurst have postulated this relationship between stillbirths, neonatal deaths, and cerebral palsy. On this basis, it is possible to broaden the concept of fetal and neonatal wastage to include cerebral palsy and possibly other related disorders.

The reduction of fetal and neonatal deaths is a very complex problem, but one of the first methods adopted by the obstetrical specialty was to define the problem. Several excellent studies have been made in leading obstetrical services and, merely selecting at random, the data of Potter, D'Esopo and Marchetti, and the obstetrical service of The Johns Hopkins Hospital are presented in Table V. This method of classification is being generally adopted by obstetrical clinics in the United States under the influence of the pioneering efforts of Potter in the field of fetal pathology. I have slightly altered the classification. A more complete classification is listed in Table VI, which has been used in this institution for the past five years (1946 to 1951). The main causes of fetal and neonatal death have been anoxia, primary prematurity, congenital malformation, and birth trauma. How similar these causes resemble the factors associated with cerebral palsy as previously described. A more pertinent analysis of the causes of neonatal death in the full-term infant can be gained from Table VII, which shows the specific causes of all full-term neonatal deaths on the Obstetrical Service of The Johns Hopkins Hospital during a thirteen-year period (1937 to 1949). Here an almost equal division between birth trauma, congenital malformations, and anoxia as causes of death occurred.

In an effort to comprehend the role of numerous factors and the causes of each fetal and neonatal death over 1,000 grams in this clinic, a Perinatal Mortality Conference (Fetal and Neonatal Mortality) was started in 1946.

TABLE V. CAUSES OF INFANT AND FETAL DEATH
(1935 to 1940)

CAUSE OF DEATH	NEW YORK LYING-IN STUDY (%)	CHICAGO LYING-IN STUDY (%)	HOPKINS STUDY (%)
Anoxia	19.8	28.7	35.7
Primary prematurity	18.5	14.4	9.6
Congenital malformation	14.1	11.1	9.6
Birth trauma	11.6	13.0	9.7
Infections	8.1	4.7	8.0
Erythroblastosis	2.8	2.2	1.6
Hemorrhagic disease	2.1	0.3	--
Syphilis	0.6	0.2	1.2
Maceration and maternal toxemia	5.2	5.3	12.7
Maceration—no toxemia	13.5	11.9	7.2
Unknown—not macerated	3.0	6.5	3.8
Miscellaneous	0.7	1.7	.8
Total mortality	3.87	4.28	4.1
Mortality of infants over 1,000 grams	3.52	3.50	3.80
Total cases (No.)	*1,000*	*1,173*	*1,043*
Stillbirths (No.)		*614*	*564*
Neonatal deaths (No.)		*559*	*479*

Each death is brought up in routine manner and discussed and evaluated as outlined in Table VIII. Experience with this type of conference has brought out many new "factors" in the evaluation of each death and a direction of thinking about the difficulties in assessing the variables that occur in the heterologous matings of the human reproductive period, as compared to a controlled animal experiment in reproduction. A list of the "possible factors" in perinatal mortality are presented in Table IX. All of these points have been previously mentioned as possible factors in the variables in perinatal mortality and should be incorporated in any study on cerebral palsy for completeness of the study. The complexities of the causes of fetal and neonatal death demand the meticulous assessment of all the clinical and physiological alterations in the prenatal and paranatal period.

In an attempt to assess the preventability of fetal and neonatal deaths a vote is recorded at the conclusion of

TABLE VI. PATHOLOGICAL CLASSIFICATION OF STILLBIRTHS AND NEONATAL DEATHS
Johns Hopkins Hospital

I. *Birth trauma*
- Intracranial hemorrhage
  - With tear of tentorium
  - With tear of falx
  - With tears of falx and tentorium
  - Without dural tear (subdural)
  - Ventricular hemorrhage
  - Subarachnoid hemorrhage
- Rupture of liver
- Rupture of other organ or vessel
- Spinal cord injury
- Edema of larynx
- Adrenal injury
- Other

II. *Anoxia*
- Abruptio placentae
- Marginal sinus rupture
- Placenta previa
- Prolapsed cord
- Rupture of cord vessel
- Other cord obstruction
- Toxemia
- Uterine inertia
- Diabetes
- Abnormal uterine contraction
- Rupture of uterus
- Intrapartum fever
- Prolonged second stage
- Hyperthyroidism
- Sickle-cell anemia
- Death of mother
- Maternal medication
- Cardiac disease

III. *Congenital malformations*
(Incompatible with life)
- Brain
- Spinal cord
- Umbilicus
- Heart
- Pulmonary
- Kidney
- Multiple
- Others

IV. *Infection*
- Pneumonia
- Oomphalitis
- Septicemia
- Meningitis
- Other

V. *Syphilis*
- Definite
- Questionable

VI. *Erythroblastosis*

VII. *Hydrops other than erythroblastosis*

VIII. *Pulmonary pathology only*
- Aspiration
- Atelectasis with hyaline membrane
- Atelectasis without hyaline membrane

IX. *Increased cerebrospinal fluid*

X. *No abnormality*
- With toxemia
- Without toxemia
- Diabetes
- Other disease

XI. *Maceration only*
(No autopsy)

XII. *Placental insufficiency*

XIII. *Therapeutic interference*
- Toxemia
- Chronic maternal disease
- Acute maternal disease
- Other

XIV. *Advanced ectopic gestation*

XV. *Other miscellaneous diseases*

TABLE VII. CAUSES OF NEONATAL DEATHS
Johns Hopkins Hospital
1937 to 1949 (over 2,500 grams)

CAUSE	DEATHS		% OF DEATHS
Birth trauma		38	22.7
Brain hemorrhage	35		
Other trauma	3		
Congenital malformation		37	22.1
Anoxia		37	22.1
Abruptio	2		
Previa	2		
Prolapsed cord	4		
Ruptured cord vessel	2		
Other cord	6		
Inertia	8		
Abnormal contraction	1		
Diabetes	5		
Intrapartum fever	7		
Abnormal pulmonary ventilation		16	9.5
Atelectasis	7		
Aspiration	9		
Infection		12	7.2
Erythroblastosis		9	5.4
Unknown		7	4.2
Unclassified		4	2.3
Miscellaneous		3	1.7
Hydrops		3	1.7
Unknown with toxemia		2	1.1
Syphilis		1	0.6
		169	

TABLE VIII. THE PERINATAL MORTALITY CONFERENCE
Johns Hopkins Hospital (October, 1946 to 1951)

Time of Conference:	4:00 P.M. Tuesday (each week).
Persons in Attendance:	Obstetrics: House Staff and Senior Staff Pediatrics: Assigned to Newborn Service Medical and Nursing Students, Visitors.
Objective:	To discuss the treatment, classification, cause of death, and preventability of each fetal loss (over 400 grams in weight and first 30 days of life) delivered in this Hospital.
Protocol:	Presentation of history: Assistant Resident, Obstetrics (assigned to laboratory).
	Discussion of clinical history.
	Discussion of pediatric care.
	Presentation of autopsy findings and placental findings—gross, x-ray and microscopic.
	Discussion of pathological findings.
	Review of case. Assignment of proper clinical and pathological classification.
	Vote on preventability.
	Vote on presence or absence of: Analgesia and anesthetic factor. Pelvic factor. Role of cesarean section in prevention of death.
	Future childbearing potentialities.

TABLE IX. POSSIBLE FACTORS IN PERINATAL MORTALITY AND FETAL SALVAGE

I. *Maternal factors*
- Age
- Race
- Height
- Weight
- Economic and social status
- Fertility characteristics
- Nutrition
- Prenatal care
- Parity
- *Pelvis*
- Maternal disease
  - Previous obstetrical history
  - Rh sensitization
  - Syphilis
  - Diabetes
  - Tuberculosis
  - Pneumonia
  - Thyroid disease
  - Liver disease
  - Heart disease
  - Kidney disease
  - Acute infections
  - Anemia
  - Rubella
  - Shock
  - Albuminuria and toxemia
- Interval between pregnancies

II. *Paternal factors*
- Age, etc.
- Sperm biology
- Nutrition

III. *Obstetrical factors*
- Presentation of fetus
- Premature rupture of membranes
- Onset of labor after rupture of membranes
- Length of labor
  - 1st stage
  - 2nd stage
- Hydramnios
- Type of delivery
- Obstetrical trauma
- Therapeutic interference
- Intrapartum infection
- Type of bacteria
- Pituitrin administration
- Type of delivery
- Skill of obstetrician

IV. *Uterine factors*
- Uterine placental blood vessel circulation
- Contraction pattern of uterus
- Muscle physiology and chemistry

V. *Fetal factors*
- Birth weight
- Respiratory factors (oxygenation)
- Breathing time (initial)
- Multiple births
- Maturity factors postmaturity
- Increased intracranial fluid pressure
- Ectopic gestation

VI. *Anesthesia and analgesia factors*
- Type of agent
- Concentration used
- Interval—duration
- Pharmacological effect of agent on fetus
- Toxicological evaluation
- Skill of anesthetist

VII. *Placental factors*
- Placenta previa
- Premature separation
- Marginal sinus
- Circumvallate
- Tumors
- Infarcts
- Placental fetal ratio
- Placental transmission of insufficiency

VIII. *Umbilical cord factors*
- Prolapse of cord
- True knots
- Vasa previa
- Rupture of cord vessel
- Hemodynamics of cord circulation

IX. *Pediatric care*
- Nursing care (nutrition)
- Facilities for premature care
- Skill of obstetrician

TABLE X. PREVENTABLE FACTORS BY VOTE OF PERINATAL MORTALITY CONFERENCE
Johns Hopkins Hospital
(1947 to 1949)

INFANT WEIGHT (GRAMS)	TOTAL ANESTHETIC FACTOR PREVENTABILITY (%)	TOTAL POSSIBLE PREVENTABILITY (%)
400-999	18.3	1.6
1,000-1,499	7.1	16.0
1,500-1,999	25.8	16.0
2,000-2,499	11.7	17.0
2,500+ (neonatal)	21.2	19.6-28.7
	PELVIC FACTOR IN NEONATAL DEATHS	
2,500+ grams	4.5% Questionable 6%	Total 10.5%

each conference. The results are illustrated in Table X. Approximately 16 to 29 per cent of the various groupings can be prevented. In a similar manner the possible analgesia and anesthesia factors were determined to be 7 to 26 per cent. If an analgesia or anesthetic factor were voted present, it merely was indicative as a possible factor and does not imply that it was the primary cause of death in each case. There are a few cases in which the members of the Perinatal Mortality Conference voted the presence of a pelvic factor, to the extent of 4.5 to 10.5 per cent of all deaths of babies over 2,500 grams delivered in the clinic.

There are undoubtedly many more important factors that operate in the causation of fetal and neonatal mortality that escape careful consideration in the light of present-day knowledge. The fetal and neonatal (perinatal) mortality conference serves as a teaching medium and as a recorder of the multiple factors involved in lethal injury. It could easily be adopted as a sound foundation upon which further knowledge in the refinement of the birth processes related to sublethal injury which may be involved in the syndrome of cerebral palsy.

It is obvious to the reader that birth injury, anoxia, congenital malformations, primary prematurity, and erythroblastosis are not only common causes of perinatal deaths but are the common causes associated with cerebral palsy. Therefore, a discussion of the progress in the current knowledge of each of these entities would be justified. I have made individual selections, since it would be impossible to review the entire literature in the space allotted to this particular subject.

PREMATURITY

It is well known that premature infants compose about one-half of the total fetal and neonatal deaths, although they comprise only 5 to 10 per cent of the total births. Two points have been apparent to all investigators in this problem. First that it is important to know why premature labor occurs, and second in importance is that many premature infants live and some die of specific causes. The causes of prematurity therefore should be considered.

Eastman in a study of 3,331 premature infants in The Johns Hopkins Hospital, delivered during the period 1926 to 1945, summarized the known causative factors of prematurity as follows:

Maternal disease, spontaneous onset	10.3%
Maternal disease, operative termination	14.3%
Congenital abnormality	1.6%
Multiple pregnancy	11.9%
Total:	38.1%

Therefore the causes of prematurity can be found in 40 per cent but in over 60 per cent no specific explanation for the accident can be elicited. The diseases most frequently responsible for the premature onset of labor are chronic hypertension, syphilis, abruptio placentae, placenta previa, heart disease, and eclampsia. Many studies including Eastman's have shown that premature labors are more common in the lower economic groups and therefore may be associated with dietary deficiencies. No final proof for these statements have been available. The most important factors in a premature infant for survival are birth weight and gestational age.

The pathological causes of premature deaths in The Johns Hopkins Hospital during the years 1937 to 1947 in infants between 1,000 and 2,499 grams were as follows:

Anoxia	28.2%
Unknown without toxemia	11.7%
Unclassified	10.1%
Trauma	8.3%
Malformation	8.3%
Atelectasis	7.2%
Maceration	7.1%
Unknown with toxemia	6.7%
Pneumonia	3.0%
Aspiration	3.0%
Other infection	2.3%
Syphilis (definite)	1.6%
Erythroblastosis	0.5%
Syphilis (questionable)	0.5%
Therapeutic interference	0.5%
Ectopic gestation	0.2%
Placental insufficiency	0.2%

It is evident that anoxia, trauma, malformation, and pulmonary difficulties are the main causes of death in the premature group.

One of the most intriguing investigations in the vast problem of prematurity is the current effort to study uterine contractility. The intricate chemistry of the muscle cell is definitely associated with not only prematurity, but also postmaturity, uterine inertia, atony, and abortion. Reynolds, one of the outstanding investigators of this problem, feels that the most fundamental point in uterine contractility is the basic understanding of the contractile system of the muscle cell. Thus Csapo has undertaken the problem of evaluation of the muscle protein, actomyosin, and its enzyme systems in smooth muscle, in both experimental animals and uterine muscle in human beings under varying conditions. This work is in a basic formative period but offers hope in the future to a better understanding of why the uterus begins contracting before 280 days of human gestation.

Some space should be devoted to the proper management of the premature labor and actual delivery. One of the generally accepted points in proper handling of the premature infant is not to narcotize or traumatize them. Heavy sedation in an attempt to delay labor after rupture of membranes is a common error. During labor no form of analgesia except caudal or spinal is justified, and delivery should be undertaken with caudal, spinal, or local infiltration anesthesia. The variable size of a premature infant's head precludes any didactic statement regarding the use of forceps. Eastman prefers median episiotomy and gentle fundal pressure for most cases, and with the larger premature infants, gentle low forceps procedures. The cord should not be clamped too soon since the premature infant needs as much blood as possible from its placental source. Following delivery, a clear airway, oxygen warmth, and excellent pediatric care will do as much as possible for the reduction of mortality and morbidity in the premature problem, in the light of present-day knowledge.

CONGENITAL MALFORMATION

The role of congenital malformation in perinatal mortality varies from about 10 to 15 per cent of the total deaths. Its exact role in cerebral palsy has not been determined but many reports would place it as the major cause. Numerous treatises such as that of Wolf, Murphy, and Gruenwald go into considerable detail on the incidence, and the general problem. It will be appropriate to use a his-

torical approach on one phase of this problem.

In the early part of this century F. P. Mall, in studying early abortuses, concluded that early dissociation of the embryo on one hand and abnormalities known as monstrosities were simply different kinds of damage, and must be produced by the same set of causes. He decided that impaired nutrition due to maternal disease was responsible for faulty implantation.

One of his students, Corner, studied 535 pregnant pigs' uteri with 3,774 embryos and recorded the following data:

1. Ten per cent of the eggs did not divide at all.
2. Ten per cent developed into blastocytes and degenerated.
3. Five to 10 per cent of embryos had died or were visibly abnormal.
4. Seventy per cent of the eggs were represented at term by living pigs.
5. No maternal disease was found in the wall of the pigs' uteri and he concluded that prenatal mortality occurs in the sow with complete absence of maternal disease. This could be determined by direct microscopic examination. Therefore, the uteri must be functionally normal with all their hormone mechanisms in good order, since at the same time they were carrying other embryos through the normal course of development.

The lethal gene concept somewhat dominated this field until the advent of the rhesus factor, maternal rubella, and many new nutritional animal experiments, such as those of Warkany, and recent oxygen experiments of Buehner and Gilman, Gilbert, and Gilman in the production of malformation by experimental embryological methods. Corner, therefore, has modified his views to conclude that the problem of embryonic defect and death in the human species is more complicated than formerly supposed. He feels that in man, as in other animals, that genetic and constitutional factors are operative in some cases, and disturbances of the maternal environment in the production of prenatal damage and loss in other cases.

It would be delightful to describe all of these new experimental approaches but only one will be described in some detail since it would appeal predominantly to an obstetrician.

In the problem of the germ cells against the environment, the difficulty of securing successful pregnancies following three spontaneous abortions (habitual abortion) is reduced to from 16 to 27 per cent if no therapy is used in the subsequent pregnancy. Jones and Delfs have conducted such a study of seventy-four pregnancies in women with habitual abortion. Repeated serum chorionic gonadotropin assays, determinations of urinary pregnanediol, basal metabolic rates, blood cholesterol, blood sugar, dextrose tolerance curves, and serum tocopherol, and analysis of husband's semen in addition to routine gynecological investigations were made. The aim of their therapy was to correct all demonstrable deficiencies. When this was accomplished, the therapeutic success was 78 per cent in future pregnancies; and 85 per cent of cases were successful in those pregnancies in which no therapeutic indications were found. Most interesting is the fact that these babies at the end of one year of follow-up are entirely normal and no congenital malformations have occurred. Benda in his study of mongolism lays great stress on the history of abortions, and other factors of poor reproductive history such as threatened abortion,

prematurity, and hormonal sterility. He advocates a period of preventive obstetrics and considers the mongoloid child as a "salvaged abortion." The work of Jones and Delfs is an interesting reply to a portion of this problem, and offers a ray of hope in the matter of practical therapeutic value in other acquired malformations. Further studies are necessary to determine how acquired anomalies may be differentiated from inherited malformations. The relation of maternal illness other than syphilis, toxoplasmosis, or rubella, as a cause, or factor, of malformation has been studied by Hartmann and Kennedy. They compared 1,228 mothers who gave birth to 1,237 infants in 1948 in which 148 were ill some time in the first trimester of pregnancy. These ill mothers subsequently gave birth to 149 children, eight of whom (5.4 per cent) had congenital abnormalities. The 1,080 mothers who were not ill in the first trimester of pregnancy gave birth to 1,088 infants of whom fifty-seven or 5.2 per cent had congenital anomalies. Thus, these authors found no significant difference between incidence of congenital anomalies following maternal illness in the first trimester of pregnancy and that following uneventful pregnancy. Landtman studying the relationship between maternal conditions during pregnancy and congenital malformations of the fetus obtained different conclusions. A positive correlation between multiparity and malformation occurred. Ante-partum hemorrhage occurred more often in pregnancies resulting in the birth of malformed children. Various morbid states such as influenza, bronchitis, sore throats, tuberculosis, mitral stenosis, diabetes, and thyrotoxicosis occurred in 42.5 per cent of the mothers who gave birth to malformed children as compared to 14.5 per cent of mothers with normal children. Landtman concluded that the relatively high incidence of various morbid states during pregnancy among mothers with malformed children has led to the assumption that these states may be involved in the pathogenesis of fetal malformations.

Erythroblastosis is said to be a combination of an inherited anomaly in which a specific type of red cell develops, and isoimmunization, hemolysis, and erythropoesis are the acquired components of the complete disease. This entity has the complication of kernicterus which is capable of producing severe cerebral defects in children who survive. Stiller followed thirty-five patients; of twenty-nine who lived, four (15 per cent) showed signs of involvement of the nervous system. McGovern and Yannet reported sixty-seven cases of asymmetric spastic cerebral palsy in which ten per cent were caused by maternal isoimmunization to the Rh factor. Evans reported eight instances (7 per cent) in which cerebral damage was due to kernicterus in 114 cases of cerebral palsy. Sobel and Wilhelm in another analysis found only 3 per cent of ninety-eight palsy children had suffered from erythroblastosis and concluded that this factor played only a small role and maternal isoimmunization was not a big factor in the total etiology of cerebral palsy. This factor needs a larger group of cases for final evaluation.

The genetic or hereditary influences undoubtedly deserve consideration but it is possible to present only a few data such as that of Pashind who

observed spastic paraplegia, epilepsy, and idiocy in three brothers in which the pregnancy and labor were presumably normal. Wilson and Wolfsohn have reported cerebral diplegia and feeble-mindedness in a pair of identical twins, with one instance on the paternal side of probable diplegia. Several other instances of cerebral birth conditions occurring in two or more members of the same family have been reported by Matthews and McDade.

In this connection a disease in ewes described as "neonatal ataxia of lambs" deserves some edification. This disease occurs in ewes of any age or breed and consists of two types of births. In the acute type the lambs are born with ataxia and in the delayed type spastic paralysis, particularly of the hind limbs, takes place two or three months following birth. Severe cases are unable to stand or walk. A paper by Innes and Shearer describes the pathology, as a diffuse, symmetrical, demyelination of the cerebrum, varying in extent from small foci in the centrum ovale to gross demyelination of the whole hemispheres, with liquefaction and cavitation in extreme cases. Secondary degeneration of the motor tracts in the cord is always present. Although the etiology is not completely solved, it appears to be related to a copper deficiency and could be prevented by administration of copper to the ewe during the gestation period.

The modern obstetrician keeps abreast of the new developments in experimental embryology, but therapy, either preventive or curative, in the human being is quite complicated. A few of the specific causes can be treated but new developments are needed in the proper understanding of the genetic, constitutional, and maternal environmental factors involved in human malformations.

BIRTH TRAUMA

It is important in any discussion of "birth trauma" to first consider a definition of the entity. Perhaps Potter has an acceptable concept in differentiating "birth trauma" from "asphyxia," since these entities could include any condition which affects the fetus adversely during labor or delivery. The simplest example is any condition which interferes with oxygen transport to the fetus producing injury to fetal tissues, and resulting in permanent tissue damage and is therefore a birth injury. Potter then distinguishes between fetal damage caused by primary inadequacy of oxygen in the circulation, and that caused by mechanical injury. In simplest terms, hemorrhage, resulting from contusions, lacerations, or fractures would be included under birth trauma and only primary oxygen insufficiency under anoxia. For purposes of this study I will limit my discussion to the hemorrhages or injuries of the brain. Traumatic hemorrhages in the cranial cavity are generally separated into three basic divisions:

1. Rupture of a meningeal blood vessel with formation of a subdural hematoma.
2. Rupture of the vein of Galen with subtentorial or generalized hemorrhage.
3. Rupture of the tentorium, with extension into the vascular sinus with the formation of either subtentorial or generalized hemorrhage.

A fourth type of hemorrhage is frequently seen in premature infants and is primarily intraventricular in type,

and varies from 2 to 8 per cent of the total types of cerebral hemorrhage. It is debatable as to whether trauma or asphyxia is the cause of this type of hemorrhage. Hemsath in a series of brain hemorrhages found only 15.7 per cent of the intraventricular hemorrhages associated with tears of the dura. For this reason in Table XI we have still included bilateral ventricular hemorrhages under the brain hemorrhage classification as a cause of death. There is every reason to believe that it may be associated with hemorrhage due to anoxia and bleeding from the choroid plexus or vena terminalis in the wall of the lateral ventricles. In our series approximately 41.3 per cent of our premature infants dying with brain hemorrhages and 21.5 per cent of full-term infants had this type of hemorrhage. This is a higher incidence than is generally reported but very few recent reports are available in the literature for comparison.

Ehrenfest in his exhaustive monograph on birth injuries did not believe that hemorrhages into the lateral ventricles occurred very often. In this extensive review of the literature previous to 1931 considerable discussion is devoted to the mechanical factors involved in the production of intracranial hemorrhage. The differential diagnosis of asphyxial hemorrhage and intracranial injury hemorrhage was difficult, according to Ehrenfest, since an engorged vein or sinus is more likely to be ruptured by an external force. Therefore, for various reasons it would be safer to regard every newborn infant not properly breathing as one likely to have been traumatized by birth.

Tears of the tentorium were regarded as an important cause of hemorrhage in the brain or meninges of the newborn infant. In Table XI, however, only 6.5 per cent of the premature infants dying with brain hemorrhage and 21.5 per cent of the full-term infants had tentorial tears associated with intracranial hemorrhage. Holland who was an avid student of this problem years ago found tentorial tears in 81 of 167 fetuses examined. In general, the incidence of intracranial injury is undoubtedly being reduced. Older data such as that of Ford which states that at least one-third of all deaths within the first two weeks of life are the result of cerebral birth injury are no longer valid.

TABLE XI. TYPES OF BRAIN HEMORRHAGE (PERINATAL DEATHS)
Johns Hopkins Hospital (over 1,000 grams)
(1937 to 1949)

INFANT WEIGHT (GRAMS)	TENTORIAL TEARS	FALX TEARS	FALX AND TENTORIAL TEAR	WITHOUT TEAR	VENTRICULAR HEMORRHAGE ONLY	TOTAL DEATHS
2,500+	11	1	1	26	11	50
2,000-2,499	1	0	1	8	7	17
1,500-1,999	2	0	0	6	3	11
1,000-1,499	0	0	0	9	9	18
Total (premature)	3 (6.5%)	0	1 (2.2%)	23 (50%)	19 (41.3%)	46
Total (over 1,000 grams)	14	1	2	49	30	96

Table XII indicates that only about 10 per cent of perinatal deaths are due to cerebral hemorrhage and probably only 20 per cent of infants born alive. Most leading obstetrical clinics have data to support this change. D'Esopo and Marchetti reported a reduction of one-half the deaths due to birth injury in the New York Lying-In and Sloane Maternity Hospitals in two groupings of their cases 1935 to 1937, inclusive, as compared with 1938 to 1940. Smith reports similar reductions in the per cent of premature and full-term stillbirths and neonatal deaths in the Boston Lying-In due to gross intracranial hemorrhage during the years 1931 to 1935 as compared with 1941 to 1945. However, an increase in asphyxial hemorrhages occurred during a fifteen-year period in which the over-all mortality was decreasing.

TABLE XII. BRAIN HEMORRHAGE PERINATAL MORTALITY
Johns Hopkins Hospital
(1937 to 1949)

INFANT WEIGHT (GRAMS)	INFANTS	DEATHS	NO.	%	DEATH RATE PER 1,000
2,500+	23,768	477	50	10.4	2.1
2,000-2,499	2,019	169	17	10.1	8.4
1,500-1,999	639	190	11	5.8	1.7
1,000-1,499	350	207	18	8.7	5.1
Total prematures	3,008	566	46	8.0	1.1
Total perinatal	26,776	1,043	96	(9.2)	3.5

One important type of brain hemorrhage which the pathologist may overlook for many reasons as a cause of death should be evaluated carefully as a possibility in the etiology of cerebral palsy. These are the hemorrhages into the brain substance itself. Schwartz first described these lesions in detail in an exhaustive treatise in 1927. He emphasized hemorrhages and areas of necrosis in the central white matter and basal ganglia of the forebrain. These structures lie close to the lateral ventricles and the hemorrhages are within the area of the tributaries of the vena magna of Galen, vena terminalis, vena lateralis ventriculi, ramus ventricularis of the vena basalis, and vena choroidea. Schwartz believed that very few infants fail to reveal at least some traces of traumatic brain lesions. Rydberg examined seventy-five newborn fetuses and found visible bleeding in fifty-eight cases, but only intracerebral or intraventricular hemorrhage in 28 per cent of the cases. He concluded that capillary bleedings are only detectable microscopically, and are very seldom absent in newborn infants. Patten and Alpers studied thirty infant brains and found punctate and large hemorrhages in the subependymal region involving the matrix area causing destruction and interference with spongioblasts. This would eventually be concerned in the deposit of myelin by virtue of their development into oligodendroglia. Patten and Alpers were unable to explain the etiology of these hemorrhages. Hemsath and Canavan studied fifty-three autopsies on newborn infants and carefully inspected the medulla in each case. In microscopic examinations of one or two sec-

tions of the medulla oblongata, there were hemorrhages in thirty-four instances (64 per cent). In twelve cases this finding supplied an anatomical cause of death which would otherwise be lacking.

Unfortunately, recent papers on this particular type of hemorrhage are difficult to find. The reasons are contingent on having meticulous examinations of the brain and adequately trained personnel. Relationships between this type of hemorrhage and future neurological sequelae are not within the scope of this paper, since considerable dispute exists in neuropathological fields regarding the pathogenesis of such lesions as status marmoratus, and other demyelinating diseases of the nervous system. The fetal and newborn pathologist must, however, make greater efforts to study these microscopical hemorrhages in greater detail so that the incidence, pathogenesis, and the exact nature of the birth processes, can be better understood and evaluated.

No discussion of the problem of birth trauma would be complete without mention of the mechanical factors involved in the methods of delivery of newborn infants. Most authorities consider malformed and contracted pelves, rigid soft parts, precipitate or prolonged labor, abnormal presentations, high forceps deliveries, breech extractions, large fetal heads, and first babies as the essential points to be considered.

Irving in 1930 demonstrated the incidence of intracranial hemorrhage associated with various types of delivery as follows:

Type of Delivery	*Incidence of Hemorrhage (%)*
Cesarean section	0.3
Normal delivery	0.4
Low forceps	0.5
Midforceps	3.0
High forceps	2.6
Breech	2.6
Version	1.7

In the past twenty years most clinics have eliminated high forceps and version, and to some degree the standard midforceps procedures. The perinatal mortality in relation to method of delivery and prematurity has been illustrated by Potter:

	% Total Deliveries	*% Mortality Related to Total Deliveries*	*% Prematures*
Natural cephalic	3.1	1.1	63.3
Low forceps	1.5	1.1	27.0
Mid- or high forceps	5.2	4.3	12.5
Version and extraction	29.3	22.0	51.0
Breech	19.8	9.3	61.0
Cesarean section	8.7	5.3	67.0
Other	69.0	40.3	56.0
Totals	4.3	2	52.3

Potter's data illustrated that premature infants need not be the significant reason for the increased mortality. It is impressive that version, breech, and cesarean section are the commonest method of delivery in the high mortality groups. Clifford in analyzing the various mechanisms of delivery on premature infants at the Boston Lying-In Hospital showed similar high neonatal mortality after breech delivery or cesarean section as compared to a definitely better record for normal delivery or low forceps. Smith in an analysis of the entire problem concluded that, breech de-

livery excluded, and weight for weight, there is very little difference between mortality and the results of common obstetrics methods of delivery.

Since it would be impossible to delve into all aspects of the mechanical side of obstetrics, and since breech delivery is not only associated with perinatal mortality but looms large in factors associated with cerebral palsy it will be singled out for special discussion.

The gross uncorrected total infantile (perinatal) mortality for breech delivery is about 20 per cent as recorded by Gordon in a study of 3,301 breech deliveries. It is apparent that this high rate is due to an increased incidence of prematurity, complications of labor, and abnormalities of the child, the presentation itself being responsible for only about one-third of the deaths. Eastman feels, however, that even in uncomplicated full-term deliveries the risk to the offspring is more than twice that associated with vertex presentations.

The predominant cause of death in breech presentations has been demonstrated in the past to tentorial tears with concurrent intracranial hemorrhage. Holland had a series in which 88 per cent of the dead fetuses after breech labors had such tears. Of course, the management of the after-coming head is the primary concern of the obstetrician in preventing these injuries. Steptoe and Moore in a study of breech presentation had a fetal mortality of 3.65 per cent for 137 infants in which forceps were used, as compared to a fetal mortality of 6.14 per cent in 228 cases in which forceps were not used.

Another problem in breech presentation is the prolapsed cord. In Moore and Steptoe's series this accident occurred in 4.85 per cent of the cases, or nine times more frequent than in all presentations. However, the type of breech, that is, frank, complete, and incomplete, is of importance to the attendant since prolapse of the cord occurs in only 0.4 per cent of the frank breech cases. In incomplete and complete breeches, prolapsed cord was twenty-two and twelve times greater. In Moore and Steptoe's series, prolapse of the cord was responsible for 53.3 per cent of the total deaths.

The actual method of delivery deserves a few comments. External version should always be attempted since it is the only preventive measure the obstetrician can execute before the actual delivery. It is generally accepted that allowing the breech to deliver spontaneously to the umbilicus has as good a mortality rate as when the infant is delivered by decomposition and extraction. In Steptoe and Moore's series the mortality rate was not increased by the length of the second stage until it was longer than one hour in the primiparas and one and a half hours in the multiparas. In general, good prenatal care, close observation during labor, conservative handling of breech deliveries, the routine use of forceps to the after-coming head and episiotomies when indicated will do much to lower the perinatal mortality rate in breech presentations. It is also possible that birth injury and anoxic neurological sequelae may also be reduced.

Of all the factors given credit for the reduction of birth injury in the past two decades, x-ray pelvimetry deserves singular mention. The pioneer studies by Caldwell and Moloy, Thoms, and Dippel have had much to do in the selection of cases for pelvic delivery

versus the abdominal route. The practical use of this adjunct remains a controversial subject among obstetricians. In Eastman's opinion, x-ray pelvimetry is essential to the management of cases of pelvic contraction for the following reasons:

1. Precision of mensuration.
When the diagonal conjugate is under 11.5 cm. this measurement is not reliable since the difference between this measurement and the obstetrical conjugate may range between 0.1 cm. and 3.1 cm.
2. Mensuration of diameters previously not obtainable—transverse of inlet; and interischial spinous diameters.
3. Stereoscopic visualization of architecture of the pelvis.
4. Evaluation of descent of head during course of labor.

Although these are distinct advantages, Eastman cautions the profession in the use of abject reliance on specific pelvic measurements to the subordination or neglect of good over-all clinical judgment. To the student of both perinatal mortality and birth injury, x-ray pelvimetry can be useful in obtaining specific facts about borderline pelvic problems. Recently Guyer and Heaton in a study of fetal risk in breech delivery pointed out that the common denominator in eight of eleven cases of birth injury due to breech delivery was a minor degree of pelvic disproportion. They advised a combined clinical and radiological evaluation of each patient with a prospective breech delivery. Even then there was no sure method for knowing whether the head will pass gently through the pelvis. These authors felt that the principal way in which fetal mortality due to breech presentation could be lowered was the recognition of cases showing slight to moderate degrees of pelvic disproportion and their treatment by elective or early cesarean section.

It should be remembered in this period of "safe" cesarean sections that this procedure is not completely free of intracranial hemorrhages. Brander in a review of the literature found seventy-two instances of intracranial lesions verified by post mortem in which the infant had been delivered by cesarean section. Ehrenfest earlier had collected nineteen such cases. Tauber described a case of Little's disease, which he ascribed to trauma at the time of the operation. Although many reports on cerebral palsy describe cases of the entity following cesarean section, only a few contain details regarding the indications for the interference. The following cases at least had the indication listed:

Author	*Indication for Section*
Gustafson and Garceau	
1. Term infant	Postmaturity
2. Term infant	Inertia
3. Term infant	Inertia
4. Premature	Eclampsia
5. Premature twins	Twins
Asher and Schonell	
1. Term infant	Maternal hemorrhage
2. Term infant	Prolapsed cord

It would be informative to have further knowledge of cases of cesarean section and the indications for abdominal delivery in understanding the specific factors relating to possible injury of the newborn infant. A group of post-mortem cesarean section babies with follow-up of their future neurological growth and development would also be interesting from the effects of the oxygen deprivation role in the etiology of cerebral palsy.

For about one hundred years there has been a hotly contested debate be-

tween pediatricians, neurologists, orthopedic surgeons, pathologists, and obstetricians on the prognosis and the etiological relations of birth trauma to numerous diseases and defects, chiefly neurological sequelae, in the future life of the child.

It is very difficult to present the widely divergent views in a judicious and impartial manner. Only a few of the studies which have been done on this difficult follow-up enterprise will be investigated. Since many investigations of this problem use the clinical term asphyxia and birth trauma synonymously, it is difficult to separate some of the studies into the broad divisions "birth trauma" or "anoxia." Many neurologists such as Ford believe it is impossible to correlate asphyxia at birth with injury to the nervous system based on clinical evidence. Ford believes that congenital diplegia is due to atrophic lobar sclerosis which in turn may be due to asphyxia, cerebral hemorrhage at birth, or degenerative or toxic processes operating in utero. His analysis of a large number of cases of typical diplegia revealed evidence of birth injury in only a small percentage of cases. Ford's recent study on birth injury consisted of thirty-three cases in which the children were born of mothers with difficult labor and symptoms of injury at birth. Only one case of congenital cerebral paraplegia developed. Hemiplegia or monoplegia associated with spasticity was the most common sequelae, with four cases of double hemiplegias with bulbar disturbances as the remainder of the cases.

Fleming evaluated thirty-three children with definite evidence of birth injury and followed for one year. Five (15.1 per cent) were abnormal at the end of a one-year follow-up. The five cases on further study were two cases of mentally defective spastic, hydrocephalic spastic, athetoid spastic, and microcephalic. Fleming felt there was no satisfactory way of determining whether the child with birth injury will recover or be permanently injured. Rydberg had a series of forty-one children who survived cerebral injury, and only ten were completely normal in later life. In a very large series of 539 newborn babies with signs of intracranial irritation, Craig observed fifty-six cases with residual mental or physical defects with forty-one of these cases also associated with cerebral palsy. In 19,052 consecutive deliveries, Roberts found 1 to 2 per cent of the infants had intracranial hemorrhage. In forty-eight children whose spinal fluid contained blood at birth only fourteen had signs of cerebral injury and only one abnormal child developed in this group. Levinson in a survey of sixty-five infants who survived cerebral hemorrhage at birth had the following sequelae:

Mental deficiency	28 cases
Mental lagging	6 cases
Periodic convulsions	6 cases
Ataxia	4 cases
Complete recovery	21 cases (32.3%)

Numerous other studies of this nature have been made but there is little information available which bears directly on many aspects of the problem. Very few studies on the late results of cerebral birth injury are above criticism. Part of the difficulty begins with the actual birth record. The modern obstetrician must be informed as to the clinical signs of early detection of central nervous system damage in the newborn infant. In general, the following symptoms should be closely looked for and the presence or absence

noted in each newborn infant's birth record:

1. Apathy or restlessness.
2. Cyanosis or pallor.
3. Bulging fontanels.
4. Convulsions or twitching tremors.
5. Difficult resuscitation.
6. Feeble high cry.
7. Irregular breathing.
8. Unequal pupils or nystagmus.
9. Poor nursing or refusal to nurse.
10. Vomiting.
11. Rapid or slow pulse.
12. Presence or absence of Moro reflex.
13. Presence of altered blood in spinal fluid.

It is imperative that major obstetrics clinics begin evaluating the newborn infant in the light of its proper neurophysiological state of health. With the advent of the neurosurgical approach on subdural hematoma as advocated by Ingraham and Matson it is imperative that early diagnosis of these lesions be made. These neurosurgeons have operated on ninety-four patients with subdural hematomas in the first two years of life. In one-third of the patients a history of traumatic delivery was elicited. In fifty-seven patients who have been adequately followed 6 months to 5 years of age, 23 per cent are retarded or grossly deficient; but 77 per cent are not only asymptomatic but show normal behavior for their age. The obstetrician is in a strategic position to suspicion the possibility of cerebral damage in the newborn infant. In addition, refinements of the mechanical side of obstetrics will continue to maintain the reductions in cerebral hemorrhages observed in all major obstetrics clinics during the past two decades. These accidents not only kill the newborn infant but may also produce sublethal injury that frequently arouse greater anguish and tragedy in the parents than death of the infant itself.

ANOXIA

For purposes of clarification, definition of the term "anoxia" is necessary since inadequate oxygen supply could be considered as the immediate cause of death in all fetuses and infants who die in the first few days of life. Potter therefore defines "anoxie" deaths as only those in which the primary causative factor lies outside the fetus. As illustrated in the pathological classification (Table VI), anoxia can be differentiated into three groups:

1. Qualitative changes in maternal blood.
   - Severe anemia.
   - Death of mother.
   - Cardiac disease.
   - Maternal medication.
   - Hyperthyroidism.
   - Toxemia.
   - Diabetes.
   - Intrapartum fever.
2. Interference with oxygenation.
   - Fetal blood in placenta.
   - Abruptio placentae.
   - Marginal sinus rupture.
   - Placenta previa.
   - Uterine inertia.
   - Prolonged second stage.
   - Abnormal uterine contraction.
3. Inability of blood to pass from placenta to fetus.
   - Prolapsed cord.
   - Rupture of cord vessel.
   - Other cord vessel obstruction.

The characteristic findings in the fetus and infants dying primarily of anoxia are small scattered petechial hemorrhages on the surfaces of the lungs, heart, and thymus. This concept has been readily accepted and adopted by many obstetric services. The anoxia deaths compose 20 to 35 per cent of the total perinatal deaths, (Table V). In Potter's analysis of 2,000 autopsies, anoxia was responsible for about the same percentage of deaths in full-term infants as in premature infants. In the Johns Hopkins Hospital a study of 1,043 deaths revealed the following

percentage of deaths due to anoxia in term infants and premature infants:

	Ante-partum	*Intra-partum*	*Neo-natal*
Premature deaths due to anoxia	23.6%	59.2%	22.6%
Term deaths due to anoxia	32.6%	63.4%	22.1%

The main causes of anoxic deaths have been complications of labor, abruptio placentae, placenta previa, and cord complications. The most specific factor in our experience has been abruptio placentae. The terms anoxia and asphyxia have been used synonymously, therefore the pathological classification advanced by Potter might not be able to completely satisfy the physiologist, since the onset of the initial extrauterine breathing mechanism is a more dynamic process than previously described. The obstetrical factors involved in the etiology of cerebral palsy could be grouped on a physiological basis as in Table XIII. This listing would allow

TABLE XIII. A CLINICAL PATHOLOGICAL CONCEPT OF THE OBSTETRICAL FACTORS IN THE ETIOLOGY OF CEREBRAL PALSY

I. *Anoxia*

A. *Anoxic Anoxia* (defective oxygenation of blood)
1. Abruptio placentae
2. Placenta previa
3. Prolapsed cord
4. Rupture of cord vessel
5. Knots in cord
6. Intrapartum fever
7. Hyperthyroidism
8. Excessive heat
9. Abnormal pulmonary ventilation
   a. Aspiration
   b. Enlarged thymus
   c. Hyaline membrane
   d. Atelectasis
10. Anesthesia in mother
    Low oxygen tension
11. Diabetes
12. Erythroblastosis
13. Placental insufficiency

B. *Anemic Anoxia* (lowered oxygen capacity of blood)
1. Rupture of uterus
2. Maternal anemia
3. Fetal anemia
4. Splenic anemia
5. Sickle-cell anemia
6. Sulfanilamide cyanosis
7. Carbon monoxide poisoning

II. *Cerebral Birth Injury*

Clinical due to:
1. Cephalopelvic disproportion (tentorial tears)
2. Excessive moulding (tears)
3. Modern theories of concussion (suction)
4. Forceps (direct trauma)
5. Intrauterine manipulation (direct trauma)
6. Breech delivery (direct trauma)

C. *Stagnant Anoxia* (slow circulation)
1. Heart disease mother
2. Hypotension in mother
   a. Spinal and caudal anesthesia
   b. Heavy sedation
3. Maternal shock
4. Death of mother
5. Prolonged second stage
6. Holding head back in second stage
7. Abnormal uterine contractions—pitocin stimulation—1st and 2nd stage
8. Forceps compression of fetal head (concussion)
9. Soft part dystocia
10. Uterine inertia

D. *Histotoxic Anoxia* (interference with intracellular oxygen exchange)
1. Analgesia
2. Toxemia
3. Biochemical imbalance
   Blood calcium
   Blood potassium
   Blood sugar
   Blood chlorides
4. Pernicious vomiting of pregnancy

Pathological types of cerebral birth injury

I. Injuries of meninges
   Extradural hemorrhage
   Subdural hemorrhage
   Subarachnoid hemorrhage
   Tentorial tears

II. Injuries of the brain
   Lacerations
   Hemorrhage
   Softenings
   Sinus thrombosis

a more dynamic and complete picture of the pathological physiology which are involved in the various clinical types of anoxia or asphyxia. It is evident that anoxia not only produces its effect through an inadequate supply of oxygen but also through a disordered circulation such as hypotension in the mother, abnormal uterine contractions and interference with intracellular oxygen exchange as associated with cyanide or barbiturates. These mechanisms are integrated with current obstetrics methods of analgesia and anesthesia. Therefore some explanation of the proper use of these drugs is mandatory in relation to the subject of anoxia in the newborn infant. Certain difficulties are encountered in obstetrics, in the administration of drugs because two physiological systems are involved. The fetus is very sensitive to drugs and has in addition a low oxygen tension. The effects of the drugs upon the respiration of the fetus appear at a lower concentration than that required to disturb the mother's respiratory mechanism. It is important to have complete safety for the mother with the anesthetic agent used, since it has been known for many hundreds of years that a baby can be delivered without anesthesia. Therefore, deaths due to anesthesia are hard to accept. The relief of pain in obstetrical procedures demands a longer period of time than in surgical procedures and often is necessary on unprepared patients. The emptying time of the stomach is delayed and vomiting frequently occurs. In addition, the pharmacological agent used must not inhibit uterine contraction. Eastman summarizes the problem of obstetrical analgesia and anesthesia as follows:

1. Obstetrical anesthesia and analgesia can, when judiciously employed, be beneficial to both infant and mother by preventing premature operative intervention. In addition, it permits more meticulous, gentle, and easier deliveries.

2. No single method is entirely satisfactory.

3. Increasing demands by a better informed mother for greater relief during childbirth.

4. The mission of the obstetrician is to relieve pain with complete safety to the mother and her child.

5. The doctor-patient relationship must be strengthened to get through as much of the first stage of labor with the minimum of pain.

6. There are many good techniques, each with advantages and disadvantages.

7. Much research is needed to properly evaluate each technique from the standpoint of its effect on the physiology of mother, labor, and fetus.

In the perinatal mortality problem it is almost impossible to assess the analgesia and anesthetic factors with scientific accuracy. In Table IX the analgesia and anesthesia factors involved in perinatal death such as the type of agent, concentration, interval and duration of action, pharmacological or toxicological effects, skill of the anesthetist are given. It is apparent that these factors are only a few of the seventy different variables (Table IX) involved in properly evaluating any single fetal or neonatal death.

Most everyone agrees that the average sedative inhibits the onset of newborn respiration, but as Smith maintains, a narcotized baby may be more acceptable than an apneic baby suffering from severe anoxia. This introduces the question of the use of the terms "asphyxia" and "apnea." Narcosis, anoxia, and brain damage have in common the clinical picture at

birth of apnea or failure to breathe in the first few minutes of life. Too many people refer to this type of baby as being "asphyxiated" and are grouped under the broad heading of asphyxia neonatorum. Eastman has condemned the use of this term, because obstetricians have taken many liberties with the term and refer to any baby who does not breathe at birth as "asphyxiated" whether the cause be lack of oxygen, narcosis, cerebral hemorrhage or congenital defect, etc. It therefore ignores the proper evaluation of a very grave cause, birth trauma, as well as the commonest cause of temporary apnea in modern obstetrical practice, namely narcosis. Therefore, Eastman proposes the use of the simple term apnea neonatorum. Irving and his associates showed that in infants born of a mother who had received neither analgesic nor anesthetic drugs, the onset of respirations occurred almost immediately in 98.1 per cent of cases. In women who received barbiturate analgesia, together with scopolamine, rectal ether, or paraldehyde, it was discovered that only 50 to 65 per cent of infants breathed immediately.

In the numerous studies on the prognosis of children who are described as apneic, or "asphyxiated" at birth, considerable doubt exists in the validity of these terms since very few observers have developed a classification in which the exact time of the initial breath or gasp was recorded. Lund, for instance, defined asphyxia neonatorum in the following manner:

	Onset Respiration
No asphyxia	Spontaneous
Mild asphyxia	1-5 minutes
Moderate asphyxia	5-15 minutes
Severe asphyxia	Over 15 minutes

In this regard, the most often quoted study on the prognosis of anoxia is that of Schreiber who studied several hundred mentally deficient children in Michigan. After excluding those cases in which the mental change occurred following brain trauma, or infection after birth, a history of apnea was obtained in 70 per cent of his cases. Schreiber's data were done in retrograde fashion and are not too clear about exact timing of the initial breath of the newborn infant. He concluded that an infant cyanotic or apneic at birth had less chances of growing up with normal intelligence than the pink baby who cried lustily when born. Schreiber admitted that he used the term apnea in its broadest sense, and did not analyze such important points as the role of dystocia, operative intervention, intracranial hemorrhage, use of oxytocics, and other factors in the anesthetics or analgesics responsible for cerebral damage at birth. Although this work was useful and provocative, it was impossible to tell what the prognosis of every apneic child would be from Schreiber's study. Therefore, the babies with severe apnea and future normal growth and development would escape detection.

Numerous studies have been made in an attempt to determine the future neurological sequelae that follow the newborn infant with apnea or asphyxia at birth. Only a few of the modern studies will be presented. McPhail and Hall in Great Falls, Montana, using a standard analgesia and anesthesia program, analyzed 1,097 consecutive deliveries in which they divided their infants into an apneic and nonapneic group. The classification of apnea was as follows:

No apnea: Color good, breathed in 30 seconds.

Mild apnea: Initial respiration delayed longer than 30 seconds, but at least one minute. Cyanosis clears with breathing.

Severe apnea: Breathing and crying longer than one minute.

In this investigation there was no difference in the intelligence quotients of the children between the nonapneic group and the apneic group. It should be mentioned that the technique of analgesia, anesthesia, and prophylactic oxygen on the newborn infants used by these authors are above average in the usual prophylactic measures in the prevention of anoxia. The second criticism is the definition of severe apnea as being a crying time and breathing time of only one minute or longer.

Darke had more rigid criteria for apnea in his group of asphyxiated children occurring in 25,000 births. He had two groups as follows:

Group I No findings.

Group II Apnea for 3 minutes or longer.

Using siblings and parents as controls, Darke found the intellectual performances of severely asphyxiated and apneic newborn infants, with no evidence of injury at birth, are significantly retarded in mental development. Keith and Norval at the Mayo Clinic, using a delay of onset of one minute as the main criteria for anoxia or asphyxia, were unable to show a serious prognosis in those infants who survived the neonatal period. Even a delay of 11 to 15 minutes before the onset of respiration, although fatal in two instances in the neonatal period, did not affect the normal growth and development in five babies. They concluded from their study that both premature and full-term infants who had asphyxia or delayed respirations either died or recovered completely and developed normally. Similar types of observations were made by Campbell, Cheeseman, and Kilpatrick, in the Royal Maternity Hospital in Belfast, Ireland. No significant differences were found in the average physical measurements, hemoglobin levels, or intelligence distributions, between a severe asphyxia neonatorum group and a control group. Their study gives no support to the hypothesis that asphyxia neonatorum is a common cause of later mental or physical retardation. Studies such as those of Preston and Doll take issue with these conclusions but unfortunately very little factual data is presented to support the view that apnea, birth injury, and asphyxia produce behavorial aspects and other allied neurological sequelae. Courville has been most prolific in the support of the idea that a number of chronic disease states which make their appearance during infancy and early childhood have their genesis in neonatal asphyxia. In this group of lesions are included cortical scars, atrophic lobar sclerosis (ulegyria), cerebral hemiatrophy, and diffuse atrophy of the brain; chronic progressive degeneration of the cerebral gray matter; porencephaly, chronic infantile cystic degeneration of the cerebral white matter; the demyelinating diseases of infancy and childhood, and the striatal diseases, such as status marmoratus and status demyelinatus. Courville feels that the inherent characteristic of the lesions themselves suggest their anoxial origin, and if his conclusion proves to be correct, the medical profession, particularly the obstetrician, must focus more attention on prophylaxis and preventia of anoxia during the pregnancy, labor and postnatal periods.

In the meantime, during the interval that this dilemma continues, the obstetrician should become acquainted with specific facts regarding the exchange of oxygen between mother and infant and the importance of close observation of the newborn infant both during labor and the critical minutes following delivery. During this interval it is his duty to provide a free and unobstructed airway by proper suction and drainage from the pharynx to the alveoli. A mixture of gases, designed and improved in the future, to satisfy the oxygen deficit that exists in the fetal blood must be used. Certain pressure devices to create the proper gradient from upper airway to the smaller radicles, the alveoli, are available and useful adjuncts. Maintenance of body warmth, slight stimulation, and avoidance of overenthusiastic resuscitation and overfeeding are the prime factors in the prevention of anoxia in the light of present-day knowledge.

DISCUSSION

A number of questions regarding the obstetrical factors involved in cerebral palsy have obviously never been answered. A great deal of work has been expended and will continue undoubtedly in future investigations. Review of the vast literature on this subject revealed at least three or four outstanding problems. One of these is the exact incidence of cerebral palsy in the United States. A study by Levin, Brightman, and Burtt in Schenectady County, N. Y., indicated that this incidence is 5.9 cases of cerebral palsy per 1,000 births. This data which is the best available estimate may not be impressive, until we compare this figure with the respective rates for perinatal deaths due to birth injury and anoxia (Table XIV). A rate of 5.9 for cerebral palsy is almost comparable to the combined rate of all deaths due to birth injury and anoxia in the Chicago Lying-In Hospital, but

TABLE XIV. COMPARISON OF INCIDENCE OF CEREBRAL PALSY TO BIRTH INJURY AND ANOXIA IN THE NEWBORN INFANT

AUTHOR	INCIDENCE	RATIO PER 1,000 BIRTHS
Cerebral palsy		
Phelps	6/100,000 population	2.5
Levin and Brightman		5.9
Birth injury		
Irving (1930)	1-2% of all children born	10-20
Alpers	0.85—2%	8.5-20
Levinson	Full term	0.45
Potter	Stillbirths	0.23
	Neonatal deaths	1.0
	Combined	1.2
Johns Hopkins Hospital	Stillbirths	0.9
	Neonatal deaths	3.0
	Combined	3.8
Anoxia		
Potter	Stillbirths	4.1
	Neonatal deaths	1.0
	Combined	5.8
Johns Hopkins Hospital	Stillbirths	9.8
	Neonatal deaths	4.1
	Combined	13.8

would be about one-third the death rate due to birth injury and anoxia per 1,000 births in the Johns Hopkins Hospital. Just as a provocative thought, the same service should be attendant on fifteen cases of cerebral palsy each year. Here lies the difficulty, and the second unanswered problem, for we are unable to find fifteen cases each year for the obvious reason that no follow-up studies are undertaken in the average obstetrical clinic. Every investigator of this problem has advocated a careful and extended follow-up on large groups of children either apneic, nonapneic, "birth injured" or "asphyxiated" at the time of the birth, and re-examinations at systematic intervals. Most workers feel that sooner or later an elaborate plan of study will have to be undertaken in both the pregnancy wastage problem, and in the cerebral palsy problem, which starts not only with the birth, fetal death, or spastic child, but rather with a large group of pregnant women from the time they first become aware of pregnancy. A few studies are now in progress. The various agencies associated with crippled children and cerebral palsy could aid a number of the leading obstetrical clinics by informing the chiefs of the services of the existence of children with these entities. Systematic reports, conducted on a yearly basis, would be most helpful in not only assessing the birth process from a fetal mortality viewpoint but also as a measuring device of the possible sublethal effects of birth injury and other obstetrical procedures. The Cerebral Palsy Case Registry as suggested by Lilienfeld and Parkhurst at a city, state, and national basis would help solve one of the most difficult problems at the present moment, that of case finding and case follow-up.

The final question which remains unanswered is the role of specific injuries such as anoxia and intracranial hemorrhage in relation to cerebral palsy. Experience with analysis of the causes of fetal and neonatal deaths has taught us that detailed clinical factors are needed to integrate and reconstruct the correct interpretation of the autopsy findings. The same difficulties which are holding up progress in the pregnancy wastage field appear also to be operative in the analysis of obstetrical factors in cerebral palsy. The problem is essentially to define and measure scientifically the specific injury and insults which produce a given injury in the birth processes during normal and pathological states. The many effects of anoxia on cortical cells of the brain, associated with vasomotor and vascular effects, are a direct challenge to medical science. Tissue injury and tissue resistance of the newborn infant to hypoxia and other alterations of oxygen chemistry await further developments in the solution of the problem. The study of perinatal pathology has progressed but it has not advanced in the study of the newborn brain. Such studies have been engrossed with the cause of death and have not been devoted to the more subtle, but less lethal lesions, which are possibly responsible for neurological sequelae following the neonatal period. Newer mechanical devices could be used in establishing the proper oxygenation of the fetus in utero and the neonate. Application of many principles in aviation medicine, and decompression sickness, as well as adult respiratory physiology, would aid in understand-

ing the proper mixtures of gases such as carbon dioxide and oxygen, and other gas pressure changes for satisfactory respiration in the newborn infant.

Fetal and neonatal mortality and cerebral palsy appear to have physiopathological similarities. Therefore, the solution of one problem may aid in the reduction of the other. A dynamic approach to both problems involves all of the multiple factors involved in the birth process and the obstetrical mechanical procedures which take place.

CONCLUSIONS

Approximately one hundred years have passed since Little associated certain obstetrical factors such as difficult labors, prematurity, and asphyxia neonatorum with the etiology of cerebral palsy. During the interim, numerous theories as to the causes of cerebral palsy have been suggested. The role of the birth processes in the production of neurological sequelae has varied from 5 to 50 per cent in previous studies on this subject. Subsequent investigations have divided the factors involved into three main groupings: prenatal, paranatal, and postnatal. Prenatal factors have been maternal trauma and disease, nausea and vomiting, hypertension, anemia, vaginal hemorrhage, abruptio placentae, placenta previa, primiparity, toxemia, and diabetes. Paranatal factors have included forceps, breech delivery, version and extraction, cesarean section, holding head back, precipitate delivery and Pituitrin stimulation. Numerous postnatal factors and child factors such as sex, twins, kernicterus, neonatal jaundice, Rh incompatibility, cyanosis, resuscitation, and convulsions were also present.

Lilienfeld and Parkhurst have demonstrated a relationship between complications of pregnancy which yield a higher combined infant loss and are also associated with mothers of cerebral palsy infants. These authors suggested the existence of a "continuum of reproductive wastage" with a lethal component consisting of abortions, stillbirths, and neonatal deaths; and a sublethal component consisting of cerebral palsy and other related conditions.

Continuing with this concept an analysis of the problems of the factors involved in the causes of fetal and neonatal deaths was made. Fetal and neonatal deaths are due to anoxia, primary prematurity, congenital malformation, and birth trauma. The similarities between the causes of perinatal deaths and the etiology of cerebral palsy were noted.

Establishment of Perinatal Mortality Conferences are excellent teaching mediums for recording numerous factors in the problem of reproductive wastage. At least seventy or more "factors" have been associated with perinatal deaths. Undoubtedly many more factors operate in both the causation of fetal and neonatal mortality and cerebral palsy.

The reduction of mortality in the premature infant has been concentrated primarily on the infant, and very little information on the causes of the onset of labor are known. About 40 per cent of prematurity is due to complications in the mother, and in 60 per cent no cause can be found. In the latter group economic and dietary factors are concerned. Studies on smooth muscle chemistry and physiology offer new hope in the problem. The method of delivery of premature infants is essentially based on the

elimination of narcosis and unnecessary trauma at the moment of birth.

Experimental embryology has new possibilities which have been reawakened in the past decade, with developments such as the rhesus factor, rubella, and the nutrition and oxygen deficiency experiments on the growing embryo and fetus. The problem in the human being is still quite complicated, but, in general, genetic, constitutional, and in a few cases disturbances of the maternal environment are capable of production of not only damage, but also death to the developing fetus.

Oversimplification of the birth process has led to improper deductions, in the past, on the subject of birth injury, to produce a literature with amazing extremes and divergence of opinion. Brain injury of the fetus has been evaluated too frequently, only as the cause of death, such as massive hemorrhage over the surface of the brain or tears and injuries of the dura. Only a few studies have been done on the more subtle injuries to the cells of the cortex, basal nuclei, and extrapyramidal tracts, which may be involved in future neurological sequelae. A general discussion of the mechanical factors involved in birth injury concentrated on breech delivery which is largely concerned not only with death due to cerebral hemorrhage, but also looms large in the numerous factors associated with cerebral palsy. Most clinics have reported a reduction of fetal and neonatal deaths due to brain hemorrhage in the past twenty years. X-ray pelvimetry and the wiser selection of cases of borderline pelvis for cesarean section are largely responsible for this reduced fetal loss due to birth injury. Numerous studies done in the past on the prognosis of birth trauma and the future development of neurological sequelae were presented. The difficulties with these studies are primarily in the lack of critical data regarding the birth process. Most of the investigations have been done in retrograde fashion, by going back ten to fifteen years to secure information from charts or birth certificates.

Anoxia deaths comprise 20 to 35 per cent of the total perinatal loss in leading American obstetrical clinics. The individual causes of anoxia have been complications of labor, abruptio, placenta previa, and cord complications. The principles of modern analgesia and anesthesia are basically concerned with absolute safety for the mother and proper oxygenation of the fetus.

Numerous studies on the prognosis of children described as apneic or asphyxiated at birth were reviewed. Some authors reported children deeply asphyxiated at birth who later on recovered completely, and other authors, with similar children, developed any number of neurological defects. The only direct approach to this problem would be to study a large group of children at birth, carefully classified as to responses to the birth process, and then, meticulous follow-up for many years with the final outcome at that time. In the meantime, the neurologist, orthopedic surgeon, pediatrician, and other various agencies in the field of cerebral palsy could interest the obstetrician by systematic reports to the obstetrical service in which each patient was born. Few obstetricians have knowledge of their cases of cerebral palsy since they are not detected in the first few months of life.

The study of perinatal pathology must be extended to include not only the knowledge of the lethal factors of the birth process, but also the sublethal factors, which may be involved in cerebral palsy. The solution of both problems are intimately related from a physiopathological viewpoint. The same unexplained difficulties which are blocking progress in the pregnancy wastage field appear to be operating in the cerebral palsy syndrome. Intricate and detailed studies of fetal tissue injury and regeneration, oxygen metabolism, and fetal respiration are needed, in order to have further reduction of the 150,000 fetal and neonatal deaths, 300,000 abortions, and the uncounted thousands of brain-damaged infants born in the United States each year.

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Clinical Conference

CONFERENCE AT COMMUNICABLE DISEASE DEPARTMENT, CHILDREN'S HOSPITAL, SAN FRANCISCO, CALIF.

EDWARD B. SHAW, M.D., PRESIDING

1. Hemophilus Influenzae Meningitis

DR. SHAW.—Dr. Cabos has reviewed for us a series of cases seen here in the last thirty years, after which we will present two cases for discussion.

DR. ELSE CABOS.—I have reviewed the cases of *Hemophilus influenzae* meningitis from 1920 to, but not including, 1951. These include a total of eighty-eight patients treated on both the staff and private services, which exemplify the improvement in end results seen during this period.

During the first of these three decades there were fourteen patients, all of whom died. During the next decade there were twelve patients among whom only one survived and this patient was hydrocephalic and mentally defective. From 1940 to 1951, sixty-two such patients were admitted. Of these, all but five survived.

The age groups of these patients conform to that generally described in the literature, fifty-nine of our patients were between 6 months and 3 years of age, the youngest was 8 days old and there was one adult of 24 years whose infection complicated a craniopharyngioma and who recovered (during the last decade) following intensive therapy and was later treated surgically.

From 1920 to 1930 the diagnosis of meningitis was established by the gross appearance of the spinal fluid, and therapy was usually begun immediately with meningococcus antitoxin which was then the only agent effective in any form of meningitis. Thereafter, when the etiology was established by bacteriological examination many different treatments were employed in a vain effort to arrest the course of the disease. These methods included repeated or continuous drainage of the spinal fluid, intravenous Mercurochrome, blood transfusion, intramuscular injection of the patient's spinal fluid, etc. These were without any effect in the course of the disease.

Between 1930 and 1940 there was improvement in bacteriological diagnosis. Anti-influenza horse serum was added to our armamentarium of treatment, but we did not have any recoveries in patients treated with this agent alone, in combination with normal human serum to provide complement, or when given with sulfonamides when these were available during the latter part of this period. The introduction of sulfonamides provided an agent which obviously affected the course of this disease beneficially although we had no survivors among the few patients who were treated with these agents alone. It was obvious, however, that patients who were treated with sulfonamides survived longer than those who made up our previous experience. Two or three children were treated with a combination of anti-influenza horse

serum and sulfonamides but these also failed to survive—these were patients in whom the disease was far advanced before hospital admission.

The rabbit anti-influenzae serum of Alexander was introduced in 1939 and came into general use in 1940. This provided an improved therapeutic agent and also a rapid and accurate means for diagnosis. The Quellung phenomenon could be demonstrated directly in the spinal fluid or in the culture of the organisms. This reaction has been employed in one case to demonstrate the presence of antibodies in the spinal fluid of a late case, using a freshly isolated strain of organisms from another source, and we have occasionally demonstrated the presence of specific carbohydrate antigen in the spinal fluid by precipitin tests with immune rabbit serum.

The last decade has witnessed a complete reversal of the dismal results of the preceding twenty years. Of the sixty-two patients admitted with this diagnosis all but five have survived. Four of these failures were those in which completely inadequate therapy had been employed for a long period before adequate therapy was instituted and the fifth patient expired within less than six hours after admission with a fulminant course resembling that sometimes seen in meningococcus disease. With the present knowledge of therapy it is possible that some of the four prolonged cases might have been saved with evacuation of loculated collections of fluid or pus in the meninges; none of these four fatalities was a recent case. In the last two years we have had no fatalities in either service or private patients, all of whom have been treated by various physicians in a fairly similar manner.

From 1920 to 1930 most of the patients expired within seven days after admission. From 1930 to 1940 the introduction of sulfonamides and serum prolonged this stay to about twenty days although there were still no survivals. In the early part of the last decade, with a high survival rate, hospital stay averaged about twenty days and this has gradually declined to a little under two weeks with the present therapy. Successful treatment initially employed rabbit serum intrathecally and intravenously with large doses of sulfonamides orally and parenterally. Streptomycin was added to therapy in 1946 and at the present time rabbit serum is employed only in those with a fulminant course, especially in infants. Routinely, the child is started with large doses of sulfadiazine subcutaneously, rather than intravenously, with the idea of establishing a prolonged sustained high level of the sulfonamides in the body fluids. Oral sulfonamides are substituted as quickly as the child will accept such therapy. Sulfadiazine therapy is continued for about two weeks in slowly decreasing dosage. Streptomycin intramuscularly is begun at about the same time as sulfadiazine in a dosage of about 100 mg. per kilo of body weight and is continued for five or six days. We do not now employ streptomycin intrathecally in this disease. Chloromycetin is the latest addition to treatment and is given as early in the disease as the child will accept oral medication or it may be administered intramuscularly. This drug may also be given intravenously although we have not thus employed

it, and it may serve as the sole therapeutic agent, but our previous results have caused us not hastily to change our scheme of therapy. Either aureomycin or terramycin has been used along with sulfadiazine and streptomycin in a very few cases without demonstrating any superiority over the treatment with sulfadiazine, streptomycin, and Chloromycetin.

DR. SHAW.—Dr. Schour will present our first case.

DR. MARIANNE SCHOUR (Assistant Resident in Communicable Diseases).—The patient is a 5-year-old boy who was admitted with a history of headache and fever twenty-four hours before admission. At 10:00 in the morning he was delirious and semicomatose, his temperature was 40° C., and examination showed marked neck and back stiffness. He arrived at the hospital early in the afternoon with a temperature of 39° C. At this time he was stuporous, screamed loudly at intervals, and showed marked nuchal rigidity. Lumbar puncture revealed a cell count of 3,400 with 82 per cent polymorphonuclears. The spinal fluid sugar was 25.1 mg. per cent; the protein was 216 mg. per cent. Smears of the spinal fluid showed pleomorphic gram-negative rods, and the Quellung test on the spinal fluid was positive for *H. influenzae* type B. Cultures of the spinal fluid and the blood were positive for the same organism.

Therapy was immediately started; streptomycin was given in divided doses to a total of 1 Gm. daily for a period of six days. Sodium sulfadiazine 3 Gm. was given during the next twelve hours intramuscularly, and the following day the patient received 5 Gm. of sodium sulfadiazine by the same route. On the third hospital day the blood level of sulfadiazine was 22 mg. per cent (a level which we consider more than adequate). Spinal fluid now showed 15,000 cells with 94 per cent polymorphonuclears, the sugar had risen to 59.3 mg. per cent, and cultures were negative although the smears still showed gram-negative rods. Spinal fluid sulfadiazine level was 15.5 mg. per cent. His general condition was now improved and he was started on oral sulfadiazine to maintain a blood level of about 10 mg. per cent.

By the fourth day of hospital stay he had regained consciousness and was later noted to have a marked herpes of the face and mouth which gradually improved.

On the seventh day of treatment, when there was good general improvement and his temperature was normal, he suddenly had a left-sided convulsion involving his face, left upper and lower extremities, and the left side of his abdomen. The convulsion was controlled by intravenous use of Pentothal and intramuscular sodium phenobarbital. This convulsion was followed by a left hemiparesis. He was believed to have a subdural collection of fluid or pus in the right motor area and a burr hole was made over the right facial motor area to explore this possibility. Nothing was discovered except moderate hyperemia of the tissue, and no localized collection of fluid or pus was found. Cultures of fluid taken at operation were negative for organisms.

Only at this time was he started on Chloromycetin intramuscularly which was continued orally when he began again to swallow. He remained

afebrile and on the ninth day of his illness, two days after the convulsion, lumbar puncture obtained a spinal fluid containing only 37 cells per cubic millimeter, 8 polymorphonuclears and 29 mononuclears. Spinal fluid sugar and protein levels were normal and the sulfadiazine level was 12.8 mg. per cent.

On this day for the first time he showed many red cells in the urinary sediment and accordingly sulfadiazine was withdrawn and he was continued on Chloromycetin alone until two weeks after onset. Five days after the appearance of left-sided weakness he attempted to stand and was found to be markedly ataxic, but this rapidly improved until the time of dismissal when there was little evident ataxia and only slight weakness of the left shoulder and hip.

The patient is now demonstrated a month after the onset of his illness. He seems alert and active and there is no remaining muscle weakness or ataxia and no defective hearing or vision. He seems to have recovered entirely.

DR. SHAW.—This child represents an infection of unusual severity in which there was good response to intensive therapy. He brings up all the problems of late sequellae which complicate modern treatment. Dr. Thelander, do you have a comment at this point?

DR. H. E. THELANDER.—When the burr hole disclosed no collection of fluid or pus subdurally and when there was no distinct evidence of residual bacterial infection, I raised the question that he might have herpes encephalitis as a complication of his bacterial disease. There was such very marked herpetic stomatitis that this seemed to me to be an interesting possibility which might be practically impossible to prove but was at least an interesting speculation. I would like to know Dr. Palmer's opinion of this hypothesis.

DR. RICHARD J. PALMER.—I did not see this child but I discussed his illness while he was in the hospital and it seemed possible to me that the findings which were noted in surgery, especially the hyperemia of the dura, indicated that he might have had a small area of cortical thrombophlebitis which accounted for the hyperemia of the cortex, the absence of any accumulation of fluid or pus, and the symptoms which he presented. This also would be difficult to prove but I think the absence of an increased spinal fluid cell count would point against the possibility of herpes encephalitis although this latter would certainly be an interesting possibility.

DR. SHAW.—You will note that our first twenty years of experience with this disease was almost devoid of complications because there was only a single survival who was complicated and had profound central nervous system damage. During the last decade with successful therapy we have encountered some late complications. Deafness has occasionally been a sequel just as it is in successfully treated meningococcus disease or even occasionally in the very benign mumps meningitis. Loculated collections of subdural fluid or pus which are refractory to chemotherapy or antibiotic agents are sometimes seen. Encephalitic sequellae which are doubtless due to vascular damage in the cortex may occur, just as they do occasionally in meningococcus disease.

That there might be secondary viral forms of encephalitis due to herpes simplex or other viral agents which may be latent in the individual as suggested by Dr. Thelander is an interesting possibility. I should like to ask Dr. Kempe to discuss some of these complications, especially the so-called hydroma or hygroma.

DR. HENRY KEMPE.—Subdural fluid collections as a complication of *H. influenzae* meningitis were described by three groups in 1948. Dr. Curnen, Dr. Olmsted, and I saw eight such patients in New Haven, and Dr. McKay in Boston described a similar number. From New Orleans came a report of similar observations during 1948. Perhaps I disagree with Dr. Shaw in his suggestion that this particular complication is largely based on the improved survival rate. Pathological reports on cases without therapy in the preantibiotic period which survived for a sufficient time, three or four weeks, to develop these changes, failed to show them. Hydromas seem to constitute a relatively new pathological entity in this purulent infection of the central nervous system. We look for hydromas in the subdural space in all children with this disease who have not been doing well in the third week of treatment and who continue with fever, irritability, frowning, failure to gain weight, or increased head size. We believe all these children should have a diagnostic subdural tap. With open fontanel and sutures this can readily be done, otherwise burr holes are required. The fluid obtained is usually thick and viscous, it may be blood tinged or deep yellow and frequently has a high protein content. Fluid is usually obtained from both sides with ease and is commonly sterile. We feel that Dr. Ingram's recommendation of gradual decompression of alternating sides daily with the removal of about 50 c.c. at each tap is an effective mode of treatment. Eventually these children require resection of the limiting membrane by neurosurgery. The cause of these complicating subdural effusions is quite uncertain. Is it possible that antibiotic therapy has changed the pathological process of the disease in a manner unknown to us? I will discuss therapy a little later when the other case is presented but I will point out that it is very hard to predict which child will develop this kind of complication except to say that a poorer specimen of child is more likely to do so. This is a fascinating subject in which the incidence of disease is quite definitely conditioned by the socioeconomic background, nutrition, and previous health records in much the same way as the factors which influence subdural hematoma following trauma.

DR. SCHOUR.—The second patient with this same disease is a 16-month-old white female. She entered with a history of neck and back stiffness and fever of four days' duration during which she had vomited once or twice. The past history was not contributory. On entry her temperature was 40.2° C. The patient was a well-developed and well-nourished child who looked acutely ill and was lethargic with grunting respirations. There was marked stiffness of the neck and back. The tendon reflexes were active and bilaterally equal. There was no cutaneous eruption and physical examination was otherwise essentially normal.

Spinal fluid showed 11,100 white blood cells with 96 per cent polymorphonuclears. Spinal fluid sugar was 31.2 mg. per cent, protein 192 mg. per cent. Smears and cultures established the presence of a gram-negative rod identified as *H. influenzae* type B. Blood count showed: hemoglobin 11.3 grams, red blood count 4.2 million, white blood count 14,150, 70.5 per cent polymorphonuclears (56.5 filamented, 14 nonfilamented), 22 lymphocytes. The urine was negative.

She was immediately started on therapy consisting of streptomycin 0.25 Gm. every four hours for twenty-four hours which was then decreased to 0.25 Gm. every six hours for three additional days. Sodium sulfadiazine 1.5 Gm. in Ringer's lactate solution was given by hypodermoclysis soon followed by oral sulfadiazine in divided doses totaling 2 Gm. per day for six days, followed by 1.3 Gm. per day for ten additional days. Chloromycetin was given in oral dosage of 1.5 Gm. per day for a total of seventeen days.

Course.—On this regime her temperature dropped from 40.2° C. to normal in forty-eight hours and she remained afebrile thereafter. Clinically she was much improved after forty-eight hours of hospitalization. Lumbar puncture was repeated on the tenth hospital day when she was believed nearly ready for dismissal. This showed 218 white blood cells per cubic millimeter, spinal fluid sugar 33.3 mg. per cent, protein 203.3 mg. per cent; smears and cultures were negative. The high protein and low sugar were disconcerting and sulfadiazine with Chloromycetin was accordingly continued for an additional seven days. On the fifteenth day the spinal fluid showed 74 white blood cells per cubic millimeter (22 per cent polymorphonuclears), the sugar was 42.2 mg. per cent, and the protein 83.3 mg. per cent; smears and cultures were negative.

Repeated urinalyses were normal and repeated blood counts rapidly returned to normal except for persistent slight secondary anemia which was treated with ferrous sulfate. Improvement continued and she left the hospital apparently perfectly well nineteen days after admission.

DR. SHAW.—The series presented by Dr. Cabos contrasts the therapy of *H. influenzae* meningitis in preantibiotic days and the results at the present time. Prior to 1937 treatment was futile; from 1937 to 1940 there was some promise of therapeutic effect with the use of sulfonamides and a slightly prolonged survival rate. Excellent results were first secured with a combination of therapeutic agents. Initially, we were successful with the use of sulfonamides combined with immune rabbit serum. The addition of streptomycin permitted gradually the discontinuance of the use of rabbit serum which is now reserved for only the more fulminant cases. It might be pointed out that in both *H. influenzae* and meningococcus infections of fulminant nature there is a place for the use of antiserum but that satisfactory serums for either infection are becoming increasingly difficult to procure.

In many bacterial infections preference is for the use of a single antibacterial agent but influenza meningitis seems to be best controlled by a combination of agents which succeeds better than either alone. I am always

reminded of the tactics of the heavyweight prize fighter of some years ago who would twine his left arm lovingly about his opponent's neck and then hit him with his right hand; this unorthodox principle of "hold and hit" seems to apply ideally to this disease. Sulfonamides alone are rarely effective but together with Chloromycetin seem to "hold" the infection by bacteriostatic action while streptomycin exerts a distinct bacteriocidal effect—the "hit" component. In mild forms of the disease any one of these agents alone will occasionally be sufficient, but this seems inacceptable as a routine because if the disease continues to smolder, the eventual problem of treatment becomes very much more difficult.

Our routine of treatment is to institute sulfonamide therapy by subcutaneous injection in large doses immediately, sometimes before the diagnosis is established with certainty. This is quickly followed by streptomycin in a daily divided dose of 100 mg. per kilo which is continued for about five days, at the end of which time bacteriological cure has usually been effected and in any event the organisms have become streptomycin resistant. Chloromycetin is coincidentally administered in a daily oral dose of 100 mg. per kilo and is continued along with decreasing doses of sulfonamides for a period of ten to fourteen days. Earlier some of these agents were administered intrathecally but we have been increasingly less concerned with this method in later years and have employed almost entirely subcutaneous and oral administration with the belief that it is principally important to saturate the tissues of the patient rather than his spinal fluid.

The results in this series have been excellent, with a single death a few hours after admission in a fulminant case and four fatalities in those with long-standing illness before admission. The series illustrates the results which may be expected in most patients encountered in private practice in which hospitalization is effected relatively early in the course of disease.

The two patients presented illustrate that even those treated by a combination of agents may be complicated. Subdural loculation of pus or fluid may require surgical intervention and at least must always be thought of when a satisfactory program of therapy does not lead to prompt improvement. Our second case illustrates the necessity for prolonged treatment even though there is an excellent clinical response when there is not prompt return of the spinal fluid chemistry to normal levels.

DR. KEMPE.—As a matter of principle in treating bacterial infections we should continue to utilize a bacteriocidal agent such as streptomycin whenever possible. A regimen which includes a sulfa drug and streptomycin with or without one of the primarily bacteriostatic agents such as Chloromycetin, aureomycin, or terramycin would seem to hold the most promise in the majority of cases. It is possible that within a few years *H. influenzae* strains will become uniformly resistant to streptomycin. A similar phenomenon has been observed with strains of *Staphylococcus aureus* treated with penicillin. Until that time streptomycin remains the

single most useful agent in this disease while the use of Chloromycetin, aureomycin, or terramycin alone must, for the present, be reserved for research centers or controlled clinical trials such as are being conducted. The plan of therapy should be to "hit them early and hit them hard."

2. Measles Encephalitis

DR. SHAW.—Dr. Jack has reviewed the unusual number of cases of measles encephalitis admitted to this hospital during the past year.

DR. OLIVE JACK (Assistant Resident in Pediatrics).—During the first six months of 1951, twenty-one cases of encephalitis complicating rubeola were seen in this hospital. Thirteen of these were from San Francisco County and the others were of a more remote origin. This is the highest incidence of this complication which has occurred in our institution. The opinion seems to be current that central nervous system complications of measles (and those of other common communicable diseases of viral origin) have become somewhat more frequent than in past years. Litvak[1] states that from 1904 to 1924 only two cases of this complication were reported among some two million cases of measles, and that by 1941 the incidence of such complications in 56,000 reported cases of measles was 1:1,000. Hoyne[2] in 1943 reported an incidence of this complication in the proportion of 1 in 642 cases of rubeola as contrasted with the previous incidence of 1 in 15,000 in 1937 and 1938. In 1951, 8,626 cases of measles were reported in this county among which there were fourteen cases of encephalomyelitis, a ratio of 1:616, but this is not significantly at variance with local experience over the past ten years. The reported number of cases of measles in 1951 was greater than any preceding time during this ten-year period.

In all probability the reporting of measles incidence is quite inaccurate and encephalitic complications are also not accurately reported, many of the latter being unrecognized if mild or are ascribed to other causes if they are severe. Furthermore, during the past ten to twenty years there has been increased interest in a variety of central nervous system infections so that the reported incidence of encephalomyelitis may very well not be comparable with that in previous times.

Among our twenty-one cases there were twelve males and nine females. The average age was 5 years, the youngest patient being 9 months of age and the oldest 8.5 years. The onset of encephalitic symptoms averaged 4.6 days after the appearance of the eruption; the earliest incidence of encephalitis (in a single case) was during the prodromal stage and the latest was ten days after the appearance of the eruption. Three of the twenty-one patients died (14.5 per cent) and eighteen survived. The surviving patients were followed by their own physicians after dismissal from the hospital so that our information is incomplete regarding the late sequellae in this series, but one was dismissed blind and another had spasticity of an extremity with the end results undetermined.

The twenty-one cases divide into those of mild nature (seven cases), moderate severity (five cases), severe (six cases), and fatal (three cases). The symptoms at onset most fre-

quently included lethargy or coma, irritability and delirium were next in frequency, and convulsions were only slightly less in frequency of occurrence. Litvak[1] reported convulsions to be the most common onset symptom and Jacobsson[5] found stupor or coma to be the most common onset symptom in his forty-eight personally reported cases.

There was little correlation between the violence of onset symptoms and subsequent course or final outcome. Similarly, the laboratory findings failed to correlate with severity of course or outcome. In nineteen patients spinal fluid examinations were carried out; six had normal cell counts and thirteen showed elevations of from 17 to 827 white blood cells per cubic millimeter.[3] The protein content was increased in eleven, sugar was increased in five and low in one, cultures were negative in all. Nearly all of the patients showed moderate elevations of the white blood counts and in no case was there persistence of the leukopenia which characterizes the eruptive stage of measles. Throughout the series no single physical sign or laboratory finding could be used as a criterion for the final outcome.

Etiology.—Litvak[4] lists the possible etiological relationship between primary infection with measles and succeeding encephalomyelitis as follows:

1. Measles virus may exhibit neurotropic characteristics.
2. A latent virus in the central nervous system may be activated in the course of measles.
3. Toxic products of infection may be localized in the central nervous system.
4. Damage to the central nervous system may be the result of an unusual antigen-antibody reaction of an allergic nature.

These theories offer little help in therapy unless the course of the underlying pathological process can be prevented or interrupted prior to the appearance of the full-blown encephalitic complication.

Therapy.—These patients require unusually skilled nursing care with their prolonged stupor and lethargy for many and obvious reasons. The accomplishment of adequate nutrition was a difficult problem met only in part and with some difficulty by parenteral injections. The patients were given parenteral fluid with suitably chosen electrolytes, dextrose, amino acids, and vitamin preparations. The use of a polyethylene nasal tube passed into the stomach was indispensable in the prolonged nutritional care of these patients who were given a formula incorporating protein concentrates, skimmed milk, carbohydrates, and supplementary vitamins, and oral medication could readily be given by this same route.

Continuous oxygen was given to about one-half of these patients, including most of the severe forms of disease. We have considered that most of these patients are anoxic to a degree which cannot be estimated by evident cyanosis or by laboratory tests, and that the nerve tissues require extreme protection against the possibility of continued anoxia.

Gamma globulin was given to three of these patients in fairly large doses without much hope that an effect on measles virus might be helpful. Pooled irradiated plasma was employed in three severe cases without any evidence of helpfulness except in the maintenance of protein metabolism.

Cortisone and ACTH were employed in five cases with the thought

that this might interfere with a possible mechanism of antigen-antibody combination. Our experience was inconclusive and the exact reasons for the employment of this therapy will doubtless be commented upon later in this discussion.

Niacinamide and nicotinic acid were employed in several patients for their vasodilating effect hoping thus to increase the blood flow through the involved brain. The results of this method were also quite inconclusive.

Case Presentation.—T. B. was a 5½-year-old white boy. The past history reveals nothing of importance. He had previously seemed to be a normal intelligent boy who was attending school. He proceeded through usual convalescence from a moderately severe attack of measles until the fourth day after the appearance of the rash when there was a sudden increase in temperature, his breathing was labored, and he responded poorly. He was admitted to the hospital promptly with a temperature of 39° C. At this time he was comatose, cyanotic, breathing deeply and rapidly, and had a slow heart rate. There was a tremor of the right arm. The eyeballs were rolling and the pupils were dilated and fixed and the fundi showed marked blurring of the discs. The neck and back showed marked stiffness, the superficial reflexes were absent, there was a bilaterally positive Babinski, the tendon reflexes were much diminished, he had priapism and urinary retention. The skin was hot and dry and showed a fading morbiliform rash without any hemorrhagic component. The lungs showed diffuse pneumonitis.

Lumbar puncture revealed a clear fluid under no increase in pressure. There were 84 white blood cells per cubic millimeter, 57 per cent polymorphonuclears. Spinal fluid protein was increased and reducing substance was normal. Culture showed no growth. White blood count was 22,000 per cubic millimeter, 94 per cent polymorphonuclears, 5 per cent lymphocytes.

The child was immediately placed in an oxygen tent where he remained for a total of twenty-eight days. During the first few days he received 10 c.c. of gamma globulin intramuscularly, 300 c.c. of pooled irradiated plasma, and dextrose and saline solutions intravenously. Chloromycetin was given in adequate dosage for the control of the pneumonitis. On the third hospital day cortisone was started by injection. Schedule was as follows:

Hospital Day	*Cortisone*
3rd	15 mg. IM
4th	200 mg. IM
5th	200 mg. IM
6th	200 mg. IM
7th	100 mg. IM
8th	100 mg. IM
9th	100 mg. IM
10th	100 mg. IM

Hospital Day	*ACTH*
10th	15 mg. IM
11th	15 mg. twice daily
12th	10 mg. twice daily
13th	5 mg. twice daily
14th	5 mg. daily
15th	5 mg. daily

During this time the patient was maintained on a low sodium diet with supplementary potassium and a Lonalac formula by polyethylene stomach tube. Physical therapy was started on the thirty-first hospital day. Some response of the patient was noted on the twentieth hospital day. Up to this time coma had continued; there was increased tonus of the right upper extremity and flaccidity of both lower extremities with absent re-

flexes. Temperature became normal on the sixth hospital day. When improvement started it was slow but continuous. He was dismissed on the sixty-third hospital day seemingly completely normal except that he was incontinent of urine and complained of headache at times. Seven and a half months after onset he seems normal in all respects and is attending school and as now shown to you seems normal in every way.

DR. SHAW.—This was one of the more severe cases in this hospital and was treated by Dr. Baumann. Dr. Baumann, would you like to tell us about this patient?

DR. F. W. BAUMANN.—This child was practically moribund when he came in and showed no signs of improvement during the first two days. He had been given gamma globulin in the somewhat vain hope that extra antibodies might benefit the course of the disease; there was no indication that this affected his course at all. The cortisone was started as a more or less desperate effort in treatment because we had no specific therapeutic agent and because of the attractive possibility that we could interrupt a curious antigen-antibody reaction in the central nervous system. Improvement was not immediately discernible and for that matter we do not know whether the improvement was due to cortisone or was completely coincidental. It seemed to me that his subsequent course was better than in many cases of comparable severity and I am at least convinced that some of the many things which we did in treatment were definitely beneficial. The polyethylene tube was invaluable in maintaining nutrition and in administering oral medication, and the use of the low sodium milk preparation with the addition of dietary supplements made it readily possible to comply with the requirements of adequate nutrition and those imposed by the administration of cortisone and ACTH.

DR. JACK.—Our second case of measles encephalomyelitis to be reported now is a 5½-year-old white female. This child had chicken pox three weeks before measles. She had had recurrent tonsillitis in the past but no other significant illnesses. Following a severe attack of measles she continued temperature elevation until the fourth day after the onset rash when she became lethargic, was deeply comatose, and was unable to take anything by mouth. She was under treatment for six days at home but then was referred into the hospital after she failed to improve. On entry she had a normal temperature. There were marked tremors of the upper extremities and of the muscles of the chest. She was unable to swallow and voided involuntarily. The pupils were unequal in size, reacted sluggishly to light, and the optic discs showed blurring of the nasal margins. There was no evidence of secondary bacterial infection throughout the respiratory tract. The upper and lower extremities on the left showed hyperactive reflexes, the Babinski was positive on the left side, the abdominal reflexes were absent.

Spinal fluid showed no increase in pressure, was somewhat bloody (trauma?), and contained 1 mononuclear cell per cubic millimeter; protein and sugar content were increased; cultures showed no growth.

The white blood count was 11,200 per cubic millimeter, 82.5 per cent polymorphonuclears.

This child was given oral cortisone for the first five days after hospital admission, beginning with 100 mg. four times a day, the dose being gradually decreased to 100 mg. on the fifth day, and this was followed by ACTH 30 mg. daily for two days, 15 mg. daily for two days, and then discontinued.

She was fed by means of an intranasal polyethylene tube which was passed into her stomach, and during her entire period when she was unresponsive and refused to swallow she was given an adequate dietary and fluid intake by this means. Potassium citrate was given in a dose of 4 Gm. daily during the period of cortisone and ACTH therapy, and during this same time Lonalac was employed as the basis for her formula. She was given niacinamide 100 mg. intramuscularly daily for eight days after the fifth hospital day. At the end of this period she was given nicotinic acid orally in a dosage of 100 to 200 mg.—sufficient to cause flushing of the skin—for a period of four days.

This child remained unresponsive for about twenty-one days. She then began to follow movement with her eyes and became somewhat irritable. She showed very slow improvement up to the time of her dismissal on the thirty-first hospital day. She gradually was able to walk and could talk a little although she was apparently quite out of touch with her surroundings. Although she obviously had some visual perception, we were quite uncertain about her vision, and inequality of pupils and blurring of the optic discs persisted up to the time of discharge. As she is presented to you today you will note that she has no recollection of her stay in the hospital, no remembrance of her trip home from the hospital, and has only gradually regained contact with her surroundings although at the present time examination of the child and conversation with her indicates that she is not notably subnormal in any respect. Her parents state that she is a little difficult to discipline but that gradually she has returned to a state which seems to them entirely normal and I think that you will all agree that her present appearance and behavior are completely different from that described during her hospital stay and would seem to promise that she will henceforth progress quite normally.

Dr. Shaw.—The two patients which we have presented this morning were among the very worst of the survivors in our series this year. This second little girl when she left the hospital resembled the later stages of the child with severe neonatal brain damage. She paid no attention to her surroundings, she showed very little evidence of useful hearing or vision, and we had most dismal forebodings for her future. She now has no memory of leaving the hospital or of anything which occurred during her hospital stay and does not even remember her trip home. All of this was only six months ago and we now present her as an extremely fortunate end result. To be sure, she has some sequellae in the way of minor behavior problems, but I believe that these are constantly improving because I saw her about a month ago and she is now very much better than she was then.

DR. THELANDER.—I particularly want to mention the opportunity which such cases give us to do group work in pediatric care. So many disciplines are involved in the management of the acute stage and in the aftercare. These patients are the concern not only of the pediatrician but also of the neurologist and the psychiatrist, and contributions are to be made by the biochemist, the physiologist, and the immunologist. These patients present us with the opportunity to study the complicated alteration in nutritional state, electrolyte balance, and oxygen exchange which attend severe central nervous system damage and permit conclusions about the visceral changes which attend damage to the central nervous system. The aftercare of these patients also provides opportunity for these various participants to pool resources for the attainment of the best final result.

DR. KEMPE.—The two patients just presented raise many fascinating points. I am struck with the fact that different epidemics of measles show marked differences in the number of complications. In some years we see many cases of appendicitis complicating the disease and in others encephalitis is disproportionately high. Well illustrated is the fact that in spite of profound coma for many days these children have made virtually complete recoveries. I have not felt that the degree of coma or number of convulsions, the electroencephalogram, spinal fluid findings, that any or all of these bear a prognostic significance. I believe we have only one criterion in giving a prognostic opinion early in this disease and that is the very fact of survival after the first week of this form of illness. We almost never lose a child who has survived a full week of measles encephalitis, at least by reason of the central nervous system disease.

The long list of therapeutic agents indicates that we have no specific therapy for this disease. You rely here on keeping the child in the best physical condition possible while he fights it out for his very life. This involves a remarkable amount of devoted nursing care and physiotherapy day in and day out, the maintenance of nutrition and fluid balance, and finally the "splinting" of damaged and edematous nervous tissue with supplemental oxygen. Dr. Thelander and Dr. Shaw have locally championed the therapeutic use of oxygen in cases of measles encephalitis for over fifteen years. They have been freely criticized for doing so by some of their local pediatric confreres who felt that "you cannot supersaturate blood with oxygen in the absence of respiratory obstruction or cyanosis." Very recently the cardiovascular group at the University of California School of Medicine and a similar group in Philadelphia have accumulated data to indicate that you can indeed do so. We consider a hemoglobin saturation of 93 per cent a very low normal value for a resting child. Quite recently we found levels of hemoglobin saturation as low as 82 to 85 per cent in sleeping normal individuals who only required awakening and subsequent activity to raise the saturation to 93 to 95 per cent. A child in coma, whatever the reason, is, from an oxygen exchange point of view, only minimally active. In a single instance we have measured

the hemoglobin saturation of oxygen in an acute case of measles encephalitis in coma and found, in the absence of respiratory obstruction or obvious cyanosis, a level of 80 per cent. Giving oxygen does what exercise does, and these levels can be raised to 95 to 98 per cent by placing the child in a maximum concentration of oxygen. Such treatment may also increase the gradient between oxygen carried in the blood and that present in the tissues which may be deficient in such a way as to allow increasing amounts of tissue oxygen to be obtained from well-saturated blood, especially if such tissue is anoxic because of edema or perivascular infiltration and hemorrhage. In addition to increasing the gradient between blood and tissue, and increasing actual hemoglobin saturation in an inactive child, the physical solution of oxygen can be increased to an amount of as much as 3 per cent of the total oxygen carried in the blood. In these three ways then more oxygen can be brought to the damaged brain in order to minimize some of the changes which at least, in part, may be due to prolonged anoxia and which are indistinguishable from it.

No one has argued very strenuously against the use of oxygen in the face of acute coronary infarction. Many clinicians feel that pain itself can be reduced by oxygen and that the eventual prognosis almost invariably is improved by oxygen therapy. Here again we are not faced with obstruction or cyanosis but merely with "supersaturation of the blood."

The use of ACTH and cortisone rates a controlled study. There is a definite possibility that some of the encephalitic changes are of a sensitivity nature and therefore may be prevented by ACTH or cortisone therapy.

An important part of definitive therapy in this disease lies in the arrangement for convalescent care; shortness of attention span, temper tantrums, night terrors, enuresis, emotionalism, and many other aspects of the postencephalitic state require a great deal of understanding on the part of the parents, relatives, schoolteachers, as well as the doctor. In general, the intelligence quotient will be found to be returned to presickness levels within six to eight months. On the other hand, behavior problems can be expected, at least in our experience, to require as long as a year or two for gradual improvement. This is the most important point and needs re-emphasis to the parents. Those parents who react violently to temper tantrums, to which they have not previously been accustomed, will increase rather than decrease the difficulty. We have recently seen five children at various times after their encephalitic state. Four of these were in homes where parents were given a good deal of understanding of the problem and who were exceedingly permissive with their children for that reason. Two of these children were not yet attending regular school. Two others received shorter school hours and all were treated in an understanding and kindly fashion with very little reaction to the occasional outbursts. These children are all improving gradually and consistently. The fifth child, on the other hand, has parents who are strict and using heart-wringing increasing strictness in the face of her present organically determined behavior disorder. This

has resulted in such a severe increase in the behavior as to make institutionalization necessary. These findings are similar to those of Dr. Byers and make it encumbent upon us to suggest reduction in ordinary demands on the part of the household, and, in general, a very permissive atmosphere and a very loving attitude for the convalescent patient with measles encephalitis.

DR. SHAW.—The house staff has an unexcelled opportunity to observe the course of disease in these patients and alert hour-to-hour care and careful attention to minor variations in course is frequently accompanied by improved end results.

Many authors group most postinfectious encephalopathies as a single syndrome but I believe that certain distinctions obtain which are governed by the primary infectious agent. This is best illustrated by the fact that encephalitis complicating chicken pox is frequently accompanied by ataxia and a predominance of cerebellar signs, whereas the encephalitis following measles shows a predilection for motor pathways and often shows paralytic components which somewhat resemble poliomyelitis. There are minor distinctions between the other forms of postinfectious encephalitis with some distinction with respect to the inciting virus.

Dr. Jack has referred to the theories of origin of postmeasles encephalitis. That the viral agent may simply be exhibiting neurotropic characteristics is best borne out by a single instance in which measles virus was isolated from the brain of a patient who succumbed after postmeasles encephalitis. I believe that most observers regard this relationship as unlikely and the latent period which usually occurs between primary symptoms of infection and the appearance of encephalitic symptoms, with the appearance of the encephalitic component at a time when the virus is presumably mostly destroyed or inactivated, would oppose this theory. In one virus infection—mumps—central nervous system complications may be due to actual invasion by the virus or may occur at a later period comparable to other forms of postinfectious encephalitis.

The second possibility that an attack of measles may provoke the manifestations of a virus latent within the central nervous system is best supported by the experimental laboratory. It is a common experience that when rabbits are injected intracerebrally with material from which it is desired to isolate a virus, the rabbit may develop encephalitic changes which prove to be due to a virus latent in the whole colony of rabbits, the injection simply having furnished a traumatic incitant. Many observers have suggested the possibility that measles infection similarly provokes symptoms due to a virus latent in the human host but this possibility seems thus far insusceptible of proof. It has pretty definitely been shown that herpes virus is not thus activated in the brain by measles and that most measles encephalitis is not herpes encephalitis.

The third possibility that toxic components of measles infection provoke encephalitic symptoms is best supported by those patients who develop these complicating symptoms early in the disease. These patients, however, do not constitute the conventional picture of postmeasles en-

cephalitis and may be entirely accounted for by those children who have neonatal damage to the brain from anoxia or other causes in which convulsions and other symptoms may be set off by infection, in the course of immunization, or may develop symptoms of central nervous system damage spontaneously. The conventional picture of postmeasles encephalitis appears after evidences of primary disease have largely subsided, four or five days after the appearance of the rash.

The fourth possibility suggested by Litvak, that an unusual antibody reaction of an allergic nature is concerned with this syndrome, is suggested by a number of things and has been commented upon by several careful observers. This type of demyelinizing encephalitis predominantly occurs in those diseases which are characterized by lifelong immunity and by extremely high levels of immune bodies in the blood. It is an attractive possibility that this high level of antibodies may attack some portion of the central nervous system which acts as a nonspecific antigen to which these antibodies attach themselves. This is not so farfetched for similar nonspecific action of antibodies is encountered in the Wassermann reaction, may be observed in the lytic effect of the serum of horses immunized against type 14 pneumococci against human erythrocytes, in the almost specific inhibiting effect of certain rabbit antipneumococcus serums in the inhibition of the growth of mumps virus in the chick embryo, etc. The phenomenon of nonspecific action of antibodies is well known and might well apply to the cauastion of measles encephalitis occurring at the time when antibody production has reached a high level. It is upon this rather tenuous theory rather than on the basis of pure empiricism that we have employed cortisone in the treatment of this condition. I do not believe that our series proves very much except that we have been somewhat fortunate in some of the severe cases thus treated.

General experience with measles encephalitis indicates an expected result of about one-third fatality, one-third recovery with severe sequellae, and one-third recovery without residual damage. It is our hope that a variety of therapeutic methods will increase the final third.

Dr. Baumann referred to the use of gamma globulin and might have included convalescent serum or pooled plasma. The acute course of measles may thus be modified almost up to the time that the rash has appeared but there seems to be no similar amelioration in the course of complicating encephalitis.

Dr. Kempe referred to the value of oxygen and defended a method which we have employed here for a long time. Our idea has been that in any severe form of encephalitis with coma, shallow respirations, impaired circulation, when oxygen levels of the blood are at minimal levels, and when a wet and damaged brain may be taking up oxygen poorly, that the least bit of increase in oxygen in the blood level might be advantageous to the condition of the child and to the eventual outcome. As a matter of fact, we have felt that the damage to the brain inflicted by the infectious process might eventually be far more reparable than that occasioned by the continued anoxia: that changes due

to demyelinization might be more readily repaired than the cellular damage of continued anoxia. I think you will agree that this thesis is tenable even though we lack a controlled series to prove the point.

The outcome in these two cases presented seems better than might have been predicted at the outset but I would be the last to propose that this sustains the use of cortisone or, for that matter, of any agent which was employed.

QUESTION.—Has measles encephalitis been reported as a complication of measles modified by gamma globulin?

DR. SHAW.—We have been looking for such cases but I believe that none has been reported—does anybody know?

DR. MAXINE SEHRING.—One such case was reported by Rosenzweig and Klugh[9] in *Pediatrics* of July, 1951. This child had been given gamma globulin at the time a sibling had measles, proceeded to develop attenuated measles after the usual incubation period, and had a moderately mild encephalitis at about the proper interval after the primary infection. These authors state that no similar case has been reported in the literature but make the comment that with the increased use of modifying agents, data on this question should be accumulated. There was a somewhat similar case in Children's Hospital of the East Bay, in which the child received gamma globulin to modify the attack but the succeeding infection was moderately severe and not much modified and was complicated with mild encephalopathy.

DR. SEHRING.—In the light of what Dr. Kempe has said about differences in complications of measles in different years, would you prefer to protect completely with gamma globulin or by careful protection against exposure in a year during which the incidence of measles encephalitis was high and then attempt to secure modification at another season?

DR. SHAW.—I am sure we all wish we knew the answer to this question. I seriously considered deliberately exposing my own 6-year-old child during the past epidemic and choosing my own time for giving gamma globulin. She settled the matter very neatly by developing severe unmodified and uncomplicated measles from unknown exposure.

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Psychologic Aspects of Pediatrics

CLUTTERING

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CLUTTERING, by which is meant rapid, confused, and j u m b l e d speech, though one of the commonest and most distinctive speech defects, has not been recognized widely in America. It is often mistaken for stuttering. The peculiar speech may be associated with abnormal clumsiness and with characteristic changes in behavior and personality. The defect persists throughout life but it can be satisfactorily controlled by p r o p e r treatment.

CLINICAL CHARACTERISTICS

The clinical characteristics of cluttering are (1) the distinctive speech, (2) motor awkwardness, (3) changes in personality and behavior, (4) association with other language defects, (5) alterations in lateral dominance, and (6) the family history.

1. The speech of the stutterer is hurried, even precipitate (tachylalia), the words seeming to tumble over one another. It is confused and difficultly comprehensible. The child starts a sentence in several different ways before he can proceed. Finally, having gotten started, he continues to mix his words and thoughts so that he ends up with a different idea from the one with which he started. Words, phrases, and even short sentences are repeated while the speaker gropes for the proper ones. Syllables and words are often omitted, in reading and writing as well as in speaking. The position of words is confused, some b e i n g inserted too early, others too late. In telling stories, there are often incomprehensible repetitions and the point of the story is lost. The clutterer has great difficulty in finding the right words and he may, consequently, get panicky while talking. Hoarseness and stammering episodes are frequent. Articulation is slurred. Overcompensation, as evidenced by unusually slow and deliberate speech, is occasionally seen.

Cluttering is unique among speech disorders in that it represents simply an exaggeration of the errors of speech made by the normal person.

The intensity of the speech defect varies. All degrees are found from speech which is simply rapid, repetitious, and slightly jumbled to almost complete incomprehensibility. Moreover, in some persons, defects in articulation like slurred s p e e c h and faulty pronunciation are more prominent, in others defects in syntax, in still others word-amnesia, and so on.

Unlike stutterers, clutterers improve their speech when they are careful and pay close attention to what they want to say. The confused speech is much less evident with strangers than under familiar circumstances with family or friends. The clutterer can remedy his

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defect if he makes a special effort. When delivering a public address he may speak flawlessly, often to the astonishment of his familiars; in contrast with stuttering, psychogenic factors play a minor role.

The late Senator Wherry of Nebraska was apparently a clutterer. According to *Time* (Dec. 10, 1951) his "words came so fast that he frequently lost control of them. A succession of 'Wherryisms' made him the Sam Goldwyn of Capitol Hill. He once promised another Senator 'opple amportunity' to make a speech, called Oregon's Junior Senator Wayne Morse, 'the distinguished Senator from Junior.' Other Wherryisms 'Chief Joints of Staff,' 'bell door ringer.' "

Probably the person best known for his cluttering was the Reverend W. A. Spooner, Warden of New College, Oxford, who had an unfortunate, or fortunate, penchant for mixing his words. The word confusions of Spooner have come to be known as spoonerisms. A spoonerism is defined in the *Oxford Dictionary* as "an accidental transposition of the initial sounds, or other parts, of two or more words." Some famous spoonerisms are:

"The two great English poets, Kelly and Sheets."

"The Lord is a shoving leopard," instead of "The Lord is a l o v i n g shepherd."

To the usher at the church wedding, "Sew her to a sheet," instead of "Show her to a seat."

2. Motor awkwardness or abnormal clumsiness (developmental apraxia) is frequently associated with cluttering as well as with other language disabilities. The apractic individual has sometimes been referred to as being ambilevous, implying that he has two left hands or is equally awkward with both hands, in contrast to the ambidextrous person who, having two right hands, is regarded as being equally skillful with both hands. The clumsiness is evident in efforts at carrying out complex movements of the hand, foot, and body. It may be associated with delayed motor development, difficulty in learning to manage buttons, tie shoelaces, handle a spoon, and other tasks.

3. Certain behavioral and personality traits have been described as characteristic of the clutterer. These resemble in many ways the deviations observed in children with cerebral damage. The clutterer tends to be hurried, easy going, erratic, and poorly organized. There may be distractibility, hyperactivity, impulsiveness, forgetfulness, untidiness, emotional instability, and ready suggestibility. The handwriting is poor and childish. By contrast the stutterer is likely to be overcareful and anxious, rigid and formal.

A feature sometimes seen in the clutterer is a striking ability to memorize poetry and even prose pieces.

4. Cluttering is frequently associated with other disorders of the language function, e.g., delay in beginning to speak, reading disability, spelling disability, and so on.

5. Alterations of lateral dominance are frequent in clutterers. There may be ambidexterity, left-handedness or crossed dominance, e.g., right-handedness and left-eyedness.

6. Family history. It is usual to find several clutterers in the same family and this occurs even when the afflicted members of the family have never met, thus eliminating the possibility of imitation. In this connection

Froeschels has pointed out that cluttering is the most difficult type of speech defect to imitate. Other types of language disability and alterations in lateral dominance are also frequent in members of the family.

Cluttering, like other disorders of the language function, is much more common in boys than in girls.

A speech defect quite like cluttering occurs in some children following meningitis or encephalitis. In these cases no family history of other language disorders or of alterations in lateral dominance is found.

PATHOGENESIS

According to Weiss cluttering is a constitutional anomaly of the language functions and is therefore to be regarded as "organic." His view is based, principally, on the hereditary nature of the deviation. He looks upon stuttering, in the majority of cases, as a further development of cluttering and therefore one finds clutterers and stutterers in the same family. But only the cluttering is hereditary, the stuttering representing the reaction of a clutterer to an unfavorable environment.

Weiss points out, further, that in many clutterers thinking proceeds without words. The patients often have the feeling that a thought process is complete before the appropriate words are present. The time interval between the appearance of the impulse to speak and the recall of the necessary words leads to the well-known repetitions and may be the origin of the various reactions which lead to the clutterer's impatience.

The early speech of children shows many of the characteristics of cluttering. Repetitions are frequent. Such expressions as ma-ma, da-da, na-na, ta-ta are typical and are characteristic up to about 4 years of age. The repetitions are of syllables rather than of letter sounds (as in the stutterer) and are unassociated with any strain. The large majority outgrow their repetitious speech but a small percentage remain as clutterers or stutterers or a combination of both.

RELATION TO STUTTERING

The most striking difference between cluttering and stuttering is that the clutterer improves his speech when he concentrates on it, indeed the defect may be completely overcome, while the stutterer's speech becomes much worse when his attention is directed to it. Consequently the clutterer speaks better in strange surroundings where he is on his guard, and he has his greatest difficulties when he is among his familiars and relaxed. The reverse is true of the stutterer who becomes tense in the presence of strangers with worsening of his speech defect; the stutterer is acutely conscious of his difficulty. Allowing the clutterer to try again makes his speech better, the stutterer's worse.

A number of cluttering children become stutterers. This is believed to take place when tension and anxiety are superimposed on the already unstable speech mechanism.

TREATMENT

Though cluttering speech is not as serious a difficulty as stuttering, it should not be regarded merely as careless or indistinct speech. The child needs to be helped to overcome his confusion.

Treatment is easier the earlier it is begun. It consists of training for self-

control and precision in speech and in social behavior. Overattention to the physiologic repetitions of early speech should, however, be avoided since it may lead to parental preoccupation with the child's speech and fixation of the repetitions. Specific points in treatment are the following:

1. Helping the child to concentrate on the details of speech and to say every word carefully.

2. Teaching the child to read every letter and not permitting substitution by association. This is best done by the reading of nonsense syllables or by reading through a small opening which permits visualization of only one letter at a time. Later this can be changed to permit visualization of one syllable or word at a time.

3. Having the child enunciate each word while writing tends to slow speech and call attention to detail.

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Comments on Current Literature

ERYTHEMA NODOSUM IN CHILDREN

WHILE erythema nodosum is a clinical manifestation that is well known to pediatricians, the true significance of this skin rash has not been clear. In a recent comprehensive review, Dr. S. A. Doxiadis (University of Sheffield, England) discusses the salient features of erythema nodosum in children, and succeeds in clarifying, particularly in his summary paragraphs, a number of the confusing and perplexing aspects of the condition. This review which appears in the December, 1951, issue of *Medicine*,[1] is the first complete review of erythema nodosum to appear since 1928.[2]

On the basis of his own observations of 100 children with erythema nodosum, Doxiadis gives the following description as characteristic of the skin rash. "The typical lesion at the beginning is bright red, raised, shiny and of an irregular round or oval shape. The size of the lesion varies from 1 cm. to 5 cm. in diameter. It is indurated and tender on palpation. Within 1-3 days the red areas become stabilised, the lesions lose their shiny appearance, they are less raised and the tenderness subsides. Then on palpation, instead of the diffuse induration of the first days, a more localised subcutaneous nodule can be felt. . . . The bright red color changes within 4-10 days to dark red and then to purple and blue. . . . The total duration of one lesion rarely exceeds 2 weeks, if the residual brownish discoloration or subcutaneous swelling is not included." The author points out that the lesions of erythema nodosum are found consistently on the anterior surface of the legs, both being involved as a rule, but not necessarily simultaneously. While characteristic lesions may occur on the posterior aspect of the lower leg and on the lateral aspect of the thigh, these locations are considered unusual. The extensor surface of the arm and forearm is second in frequency after the lower limbs. Involvement of other portions of the body is rare.

In addition to the characteristic skin manifestations, elevation in body temperature usually occurs some time during the clinical course of the skin rash. Sore throat frequently precedes the eruption, and a history of joint pains and occasional joint swellings associated with erythema nodosum is not uncommon. Lymphadenopathy, particularly in the cervical and supraclavicular regions, has been reported in a number of children.

Extensive laboratory studies have been carried out on patients suffering from this condition. Concerning the blood picture nothing characteristic has been encountered, with the exception that in practically all the cases studied, the red cell sedimentation rate was elevated significantly. The very marked female preponderance which has been reported after puberty does not seem to be as striking in the pediatric age group, although on the basis of the statistics available, Doxiadis concluded that even in childhood a higher incidence of erythema nodosum does occur in females.

While the patient with erythema nodosum usually shows rather dramatic findings, easily recognized clinically, the significance of such a skin rash from the standpoint of the etiological factors involved has presented serious problems in diagnosis, particularly since the diagnoses to be considered have serious implications so far as therapy and prognosis are

concerned. There appears to be no question that a close relationship exists between erythema nodosum and infection. However, the nature of this relationship, the type of infection, and the prognostic import of the skin rash have not been defined clearly.

In years past the role of tuberculosis in the etiology of erythema nodosum was stressed, and, at one time, all cases of erythema nodosum were thought to be associated with tuberculous infection. Although it is now clear that erythema nodosum may be associated with infections other than tuberculosis, it is evident that a larger proportion of children with erythema nodosum does have tuberculosis, than do other children of the same age. The occurrence of erythema nodosoum has been related also to the presence of infection with beta-hemolytic streptococcus. The clinical observations reported have been supported by laboratory studies which point to a definite relationship between beta-hemolytic streptococcus infection and the occurrence of the skin rash. In this connection it is interesting to note the feeling of the author that erythema nodosum and rheumatic fever may both occur as the result of given streptococcal infections, and that they may therefore be coincident without erythema nodosum being a manifestation of rheumatic fever. This view is not in accord with that of some authors who consider erythema nodosum a manifestation of acute rheumatic fever.

The occurrence of what appears to be typical erythema nodosum in cases of coccidioidomycosis (infection with the fungus, *Coccidioides immitis*), has served to emphasize the relationship between another type of infection and the presence of skin manifestations which may be characteristic of the classical clinical picture of erythema nodosum. Observations on the conversion of coccidioidin tests from negative to positive during the clinical course of coccidioidomycosis, the isolation of fungi from the patient with this disease, correlated with the skin manifestations, have served to clarify in a rather unique way some of the basic features of the erythema nodosum skin rash.

At the close of the section on etiology the author attempts to evaluate the importance of the specific infections responsible for erythema nodosum, including possible virus infections, but fails to find confirmation of any true specificity in the recorded clinical impressions. Wisely he summarizes the section by stating that this condition represents a nonspecific syndrome occurring during the active stage of various infections, and that the relative importance of the specific infection differs from country to country. In Europe and South America the commonest infection associated with erythema nodosum seems to be tuberculous, in North America that with beta-hemolytic streptococcus, and in certain restricted areas in the United States, coccidioidomycosis. This conclusion tends to support the conception, stated frequently in the past, that the skin manifestations which characterize erythema nodosum, may be brought about by any generalized infection.

In a section devoted to the pathogenesis of erythema nodosum, Doxiadis gives an excellent summary of what is known concerning this confusing subject. He emphasizes the fact that the histologic picture of the lesions in erythema nodosum appears to be the same, whatever the causative agent. From a careful study of published reports, the author points out that, while tubercle bacilli have been demonstrated in the lesions of erythema nodosum in a few cases which were associated with tuberculous infection, there is no unequivocal report of the presence of beta-hemolytic streptococci or *C. immitis* in the lesions of patients with erythema nodosum where the condition was associated with infections due to these organisms. Yet in all three conditions the lesions characterizing the erythe-

ma nodosum appear to present an identical pathogenesis. Thus it seems reasonable to Doxiadis that a state of hypersensitivity is responsible for the development of the skin lesions, and not the presence of the infectious agent locally. He makes the interesting point that there is a marked similarity between a positive intradermal tuberculin reaction and a lesion characteristic of erythema nodosum, an observation which lends support to the conception that the skin lesion in erythema nodosum is developed on a hypersensitivity basis.

The pathogenesis of the skin lesion is described in considerable detail by the author and is well illustrated by photomicrographs of pathological material. In the first few days the lesion presents a histologic picture of acute inflammation with hyperemia, edema, and infiltration of polymorphonuclear leukocytes, which may be marked but never leads to suppuration. Later these initial signs of acute inflammation subside and fibrinoid degeneration of the collagenous connective tissue makes its appearance. Finally, nonspecific chronic granulomatous foci appear. In some sections of the lesions giant cells of the foreign-body type may be seen; these occur in young lesions of three days' duration and also in older lesions, as long as two months later. The granulomatous nodules are of particular interest, having a rather characteristic appearance in the various stages of their development. These nodules which appear very early in the inflammatory process consist of closely aggregated mononuclear cells, probably histiocytes, proliferated locally, the oval nuclei of which are disposed radially around a central cleft. These granulomatous nodules occur singly, or in groups, in close association with fat lobules, or in swollen fibrous septa. In early lesions, as of twelve hours' duration, many polymorphonuclear leukocytes accompany the proliferating histiocytes. As the lesions progress the clefts are more marked. A high-power study of a four-day-old lesion reveals well-developed nodules and characteristic clefts with many histiocytes arranged radially around the axial clefts. In none of these lesions have bacteria been described.

This exhaustive review covering an interesting and important subject in pediatrics is a welcome one, especially since there has been considerable confusion concerning the significance of erythema nodosum. While nonspecific in nature, this skin rash of characteristic appearance has been associated with serious diseases such as tuberculosis, streptococcal infections, rheumatic fever, and coccidioidomycosis, and its presence should focus attention on these diagnostic possibilities. The most satisfactory interpretation seems to be that erythema nodosum can occur in any infectious disease, the cutaneous manifestations being, in all probability, on the basis of hypersensitivity. The relationship between provocation and the development of erythema nodosum is of interest in connection with sulfonamide therapy; sulfathiazole, particularly, has been shown to be a potent provocative agent in bringing about this skin manifestation in a patient who is suffering from tuberculous infection, or infection with hemolytic streptococci, and who has the capacity to react in this manner.

RUSSELL J. BLATTNER.

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News and Notes

Dr. Charles U. Lowe of the University of Minnesota has been appointed professor of pediatrics at the University of Buffalo School of Medicine. Dr. Lowe will be in charge of the laboratories at the Children's Hospital.

The first issue of a new special journal **Metabolism** was published in January. It is edited by Dr. Samuel Soskin of Chicago, and will be published bimonthly by Grune & Stratton. Dr. Irvine McQuarrie is a member of the Editorial Board.

Among the grants recently made by the **National Foundation for Infantile Paralysis** for virus research were $26,525 to the Children's Hospital, Boston, Dr. John F. Enders; $86,300 to the Children's Research Foundation, Cincinnati, Dr. Albert B. Sabin, and $17,710 to Stanford University, San Francisco, Dr. John A. Anderson. A grant of $10,000 was made to the Academy of Pediatrics to increase the number of skilled professional workers.

A **Summer Camp for Diabetic Children** will be opened for the fourth season under the auspices of The Chicago Diabetes Association, Inc., from July 1 to 22, 1952, at Holiday Home, Lake Geneva, Wis. In addition to the regular personnel of the camp, there will be a staff of dietitians and resident physicians, trained in the care of diabetic children, furnished by The Chicago Diabetes Association. Boys and girls, aged 8 to 14 years, inclusive, will be accepted. Inquiries as to applications and fees should be addressed to Service Unit, Chicago Diabetes Association, 110 S. Dearborn St., Chicago 3, Ill.

A two-week **Postgraduate Course in General Pediatrics,** Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, under the auspices of the Harvard Medical School and direction of Dr. Allan M. Butler, professor of pediatrics, June 9 through 21, 1952. Clinics providing a broad review of pediatrics emphasizing the new advances will be given daily from 9:00 A.M. to 4:30 P.M. by selected authorities from the Pediatric and Specialty Services of the Massachusetts General Hospital, the Ophthalmological and Otolaryngological Services of the Massachusetts Eye and Ear Infirmary and the Children's Medical Center, Boston. For further information write: Assistant Dean, Courses for Graduates, Harvard Medical School, 25 Shattuck St., Boston, Mass.

The **University of Minnesota** will present a course in Pediatrics on April 21 to 23, 1952. The course will be presented at the Center for Continuation Study and is intended primarily for physicians specializing in pediatrics. Emphasis will be placed on infectious diseases as they occur in pediatric practice. Dr. John M. Adams, professor, department of pediatrics, University of California, Los Angeles, formerly a member of the department of pediatrics at the University of Minnesota, will be the visiting faculty member for the course. Dr. Adams will also deliver the annual Clarence M. Jackson lecture sponsored by the Phi Beta Pi Medical Fraternity on the subject of "Respiratory Diseases—Changing Concepts."

The 28th Annual Meeting of the **Alabama State Pediatric Society** will be dedicated to **Dr. Alfred A. Walker,** who is called the Father of Pediatrics in the State of Alabama. The meeting will be held in Montgomery, Ala., on April 16, 1952. The scientific speakers will be Dr. Francis F. Schwentker and Dr. William A. Reilly. Dr. Hughes Kennedy, of Birmingham, Ala., will give the address of Tribute to Dr. Walker. Pediatricians and Dr. Walker's friends are cordially invited to attend this meeting.

Book Reviews

Differentialdiagnostische Symptomatologie von Krankheiten des Kindesalters. Prof. Dr. W. Catel, Stuttgart, 1951, Georg Thieme Verlag (Grune and Stratton, New York agents for U. S. A.), 640 pages. Price DM 69.

There is nothing quite comparable in English in plan or in scope to this text on

differential diagnosis of the diseases of childhood based on symptomatology. The subjects discussed are divided into thirty-six chapters. The first three, for example, discuss the conditions in which there is a failure of normal growth (Minderwuchs) such as cretinism, the chondrodystrophies, and celiac infantilism. Other chapters present a discussion of the conditions presenting such symptoms or findings as hypertension and hypotension, cardiac arrythmias, anemia, cervical adenitis, vomiting, abdominal pain, paralysis, and convulsions. There is a certain unevenness in the discussions, and the relative importance of the conditions discussed is decidedly "geographic" at times. Thus under the anemias a brief paragraph on sickle-cell anemia concludes with the statement that the disease is without practical importance. Another insularity in the text is that practically no references are given except to German medical literature. For example, although Mediterranean anemia or thalassemia is discussed under the term "Cooley's anemia," there is no reference to Cooley's publications in the bibliography attached to the chapters on anemia.

Despite these shortcomings, the book contains a vast amount of material which should be of considerable help in a pediatric departmental library as a book of reference for the staff and house officers. The chapters on alterations in growth, and particularly the chapters discussing differential diagnosis on symptoms relating to diseases of the nervous system, are in the opinion of the reviewer the best in the text. The book is excellently printed and contains many good illustrations and numerous tables relating to differential diagnosis.

Topographische Ausdeutung der Bronchien im Röntgenbild mit Berücksichtigung der neuzeitlichen Nomenklatur. Claus Esser, Stuttgart, 1951, Georg Thieme, 152 pages, 77 illustrations. Price DM 33.

This book presents the results of an anatomical-roentgen correlation study of bronchial anatomy as demonstrated by bronchography and laminagraphy. Although no original work is included, the author does present an excellent compendium of the existing literature on the subject. The arrangement of the material under separate headings for each bronchus makes for easy reference. The listing of all the terminology for the same bronchus as used by different authors is extremely helpful to anyone trying to correlate the confusion of nomenclature in the literature. The author uses the terminology of Boyden for the segmental bronchi.

The chief virtue of this publication lies in the illustrations, which, except for the disadvantage of being negative prints, are of excellent technical quality. They nicely demonstrate anatomical detail and constitute a roentgen counterpart to the anatomical studies of Boyden, Brock, and Jackson and Huber. To radiologists, thoracic surgeons, and anyone interested in bronchial anatomy this book is recommended. Those who do not read German fluently can still obtain most of the meat of this book by carefully scrutinizing the illustrations. SEAMAN.

Tonsil and Allied Problems. Roy H. Parkinson, M.D., F.A.C.S., New York, 1951, The Macmillan Co., 432 pages. Price $12.00.

Parkinson presents a book containing meticulous detail of the embryology, anatomy, pathology, physiology, and surgery of the tonsil. The anatomical discussion and the many very excellent illustrations of the anatomy of the tonsil and associated structures make it a very desirable text for the student and a pleasurable review for the otolaryngologist as well as the general practitioner. The embryological development and the histology of the tonsil are thoroughly covered in an interesting way. A clear and concise coverage of the pathological processes involving the tonsil is presented. Technique of tonsillectomy is presented simply with more excellent illustrations, and postoperative complications are fully discussed. The book will be of great interest to all who deal with the tonsils and their problems. HANSEL.

Modern Medication of the Ear, Nose and Throat. Noah D. Fabricant, M.D., M.S., New York, 1951, Grune & Stratton, 245 pages.

This represents an effort to present in simple form the treatment of various phases of otolaryngologic conditions and results in a handbook for which the general practitioner will have much use. A simple concise discussion of various common otolaryngologic conditions is presented along with a few suggested forms of therapy. It is felt that oversimplification detracts somewhat from the author's original aim; however, in this period of increased therapeusis in the field of otolaryngology it will be found to be a useful book by many. HANSEL.

Editor's Column

PEDIATRICIANS AND MALPRACTICE

WHILE actions for malpractice are far less likely to be brought against pediatricians than against their surgical colleagues, the fact that they are dealing with minors from the legal standpoint creates certain definite responsibilities and liabilities. Malpractice suits have become much more frequent in recent years. In 1950-1951 during a twelve-month period, 205 new malpractice actions against physicians were instituted in New York State.

The law requires that a physician must possess and exercise the knowledge and skill which is commonly possessed and exercised by other reputable practitioners in his field, in the community in which he lives. In the case of pediatricians (or other specialists) this would presume a responsibility which would be in excess of that of the general practitioner, in the medical care of children. The law also implies that experimentation may be considered as malpractice under certain circumstances. It is probably unwise to create the impression in the parents' minds that you are trying out a new procedure or a new drug.

When the pediatrician once accepts the care of a given case, he is responsible for the completion of that case, whether or not he desires to continue. He is legally permitted to withdraw from the case only after due notice is given to the family, and only if there is a reasonable certainty that adequate medical care will be otherwise obtained. The family has the privilege of discharging the physician at any time that they so desire, but for his protection it would be wise to have this understanding verified either in writing or by witnesses, should such a procedure take place in the course of a potentially dangerous illness.

For all operative procedures, and for diagnostic procedures which are even remotely attended by a risk, the pediatrician should always have the parents' consent in writing. If the parents are not available for some reason, such as their absence from town, consent should be obtained from the closest available relative. If no relative is available, even in an emergency, or a lifesaving situation, medical consultation and agreement on the necessity of immediate operative interference should be obtained.

When a child is brought to you with a history of injury and signs which could in any way suggest a fracture or dislocation, you can only be fully protected from a malpractice standpoint if you have the part examined by x-ray. Pediatricians are cautioned against relying upon fluoroscopic examinations in such cases.

The question of tetanus antitoxin poses a problem. There are many

physicians who believe that tetanus antitoxin, as routinely used after accidents, is of questionable necessity or even value. It is probable, however, that in most localities it would be considered proper by the majority of physicians. This imposes a real risk when the individual physician neglects to administer it in a given case without the written agreement of the parents. The avoidance of this problem is simple and can be accomplished by the routine active immunization of all children with tetanus toxoid before the age at which they are likely to be injured. With regard to other immunization procedures and the treatment of acute disease by specific immunological agents, the same principles would apply. Caution should be given with regard to the use of foreign protein substances in the treatment of disease. It is probable that the physician would be liable if he did not exercise reasonable care in an effort to prevent anaphylactic shock.

The insurance carriers can easily prove that a large number of malpractice suits originate directly as a result of a careless remark on the part of one doctor implying or stating carelessness on the part of another doctor. In this respect, pediatricians should be very careful what they say to the parents with regard to the handling of the case by the general practitioner before the pediatrician sees the child. Remember that "damning by faint praise" frequently is more dangerous than outright disapproval. It is our belief that no physician ever gained by derogatory implications regarding the status of one of his contemporaries.

R. A. HIGGONS.

CEREBRAL PALSY

MANY of the great causes of death among infants and children have been or are being rapidly conquered, and few indeed are the infants and children born today who need die in early life. It is obvious that more attention needs to be devoted to the incapacitating rather than killing diseases, so that children may grow up to be strong, healthy citizens, mentally and psychologically normal, and not handicapped by physical ailments. Among the larger groups of children with incapacitating disorders are those with cerebral palsy, sometimes in association with convulsive disorders and mental retardation. A very conservative estimate would be that at least one out of every 150 children has an incapacitating neurological handicap consisting of cerebral palsy, either singly or in combination with a convulsive disorder or mental retardation. Can we with the resources available make these patients into useful citizens? It is only with increasing interest among the medical and allied professions in the problems of handicapped children that progress will come, first in a better understanding of the disorders, later in development of better methods of prevention and treatment.

The Research Council of United Cerebral Palsy Associations under chairmanship of Dr. Sidney Farber is conducting a series of symposiums to review various phases of the problem of cerebral palsy. Manuscripts presented at the second research symposium held in Philadelphia on Nov. 2, 1951, appear in this and two subsequent issues in THE JOURNAL OF PEDIATRICS. The first of these papers by

Dr. Anderson reviews obstetrical factors in cerebral palsy. The second, by Dr. Hughes, discusses the electroencephalographic follow-up of children with birth injuries. The third paper, by Dr. Palmer, deals with speech disorders and speech training in children with cerebral injuries. The rest of the symposium is devoted to a summary of those directions deemed important in research. An interesting contribution in this field is that of Dr. Hicks on the effect of radiation of the mother and administration of drugs to the mother in the production of deformities in the fetus in experiments with animals. Dr. Hicks received the Max Weinstein Award of the United Cerebral Palsy Association for the outstanding contribution of 1951 in fundamental research toward a better understanding of cerebral injuries.

Very few cases of cerebral palsy are due to hereditary causes. This is fortunate, since hereditary defects in the brain cannot, with our present knowledge, be prevented. While there can be no doubt that adverse conditions of oxygen supply, nutriment, and infection in the mother may injure the developing brain of the unborn infant, the proportion of injuries due to these things, in relation to the total number of defects due to other causes, appears small. Furthermore, we do not at this time know how to prevent developmental defects. Injury to the fully formed brain may occur before birth, but numerically the largest groups of handicaps in children are due to injury or anoxia during the birth process. This is important because here much can be done in prevention. Indeed the work of many investigators indicates that birth injuries are singularly the second most important cause of mental defect and probably the first cause of cerebral palsy. The contribution of Rh incompatibility between mother and child has recently come into prominence as a cause of mental retardation and cerebral palsy in infants. Despite our best efforts in treatment, many of these infants suffer severe and permanent damage to the brain. Postnatal accidents, injuries, or infections contribute a sizable number of cases of cerebral palsy. Of all of these causes, only injury at birth and postnatal factors are controllable in other than the exceptional case. Thus any sizable reduction in the incidence of cerebral palsy must be obtained by the attack on these two factors—birth injury and postnatal injury and infection. But while attempts are being made to prevent cerebral palsy, thus diminishing the numbers of these patients, are the existing facilities for the treatment of cerebral palsy satisfactory? Cerebral palsy cannot be cured. However, more could be done for the person with cerebral palsy if more knowledge were available concerning causation, prevention, early recognition, and treatment, and if better techniques were developed for speech, physical and occupational therapy—goals that appear to be attainable through research. Another research symposium soon to be held will attempt "an objective appraisal of the present method of treatment of cerebral palsy."

C. F. McK.